Review

Effects of Pulsed Electromagnetic Field Therapy on Pain, Stiffness, Physical Function, and Quality of Life in Patients With Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

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Objective. Pulsed electromagnetic field (PEMF) therapy is a potentially useful treatment for osteoarthritis (OA), but its effectiveness is still controversial. This study aimed to examine the effects of PEMF therapy and PEMF parameters on symptoms and quality of life (QOL) in patients with OA.

Methods. Cochrane Central Register of Controlled Trials, PubMed, CINAHL, EMBASE, PEDro, clinical trial registers, and reference lists were searched until April 2019. This study examined randomized, placebo-controlled trials, patients with OA, symptom and/or QOL related outcomes, and articles published in English. Two authors extracted data and completed quality assessment.

Results. Sixteen studies were included in our systematic review, while 15 studies with complete data were included in the meta-analysis. Our primary outcome was the standardized mean difference, which was equal to the treatment effect in the PEMF group minus the treatment effect in the placebo group divided by the pooled standard deviation. For pain, the standardized mean difference was 1.06 (95% CI = 0.61 to 1.51), for stiffness 0.37 (95% CI = 0.07 to 0.67), for function 0.46 (95% CI = 0.14 to 0.78), and for QOL 1.49 (95% CI = −0.06 to 3.04). PEMF parameters did not influence symptoms.

Conclusions. Compared with placebo, there was a beneficial effect of PEMF therapy on pain, stiffness, and physical function in patients with OA. Duration of treatment may not be a critical factor in pain management. Further studies are required to confirm the effects of PEMF therapy on QOL.

Impact. Our study suggests that PEMF therapy has clinically significant effects on pain in patients with OA. The current evidence was limited to the short-term effects of PEMF therapy.

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Osteoarthritis (OA) is a chronic degenerative joint disease that occurs most commonly in people over 45 years. OA is characterized by articular cartilage loss, synovial inflammation, and the remodeling of subchondral bone.[1] OA has been shown to be associated with joint pain,[2] stiffness,[3] loss of function,[4] reduced quality of life (QOL),[5] and mortality.[6,7] OA affects up to 240 million people globally, approximately 10% of men and approximately 18% of women over 60 years of age.[8] Treatment of OA traditionally comprises nonpharmacological and pharmacological management, though if symptoms persist, surgery may be considered.[9] Current treatments for OA are limited by small effect sizes and adverse side effects. In recent years, there has been much emphasis on nonpharmacological management such as education, physiotherapy, and exercise therapy to relieve symptoms and improve function in those with OA.[9–12]

Pulsed electromagnetic field (PEMF) therapy, which uses a time-varying magnetic field generated by electrical current passing through a conductor,[13] has been proposed as a potential treatment for OA. PEMF therapy has been shown to prevent cartilage degeneration[14] and maintain subchondral trabecular bone microarchitecture.[15] Further, there is some evidence to suggest that PEMF therapy may reduce pain in those with OA by limiting the catabolic effects of pro-inflammatory cytokines[16] and increasing extracellular matrix production,[17] cytokine release, and chondrocyte proliferation.[18]

Evidence from previous systematic reviews is conflicting. A previous systematic review by Li et al suggested that PEMF therapy may reduce pain but was ineffective in improving physical function and QOL in those with OA.[19] In contrast, 2 separate systematic reviews, by Negm et al and Ryang et al, showed that PEMF therapy was effective in improving physical function but did not reduce pain in those with knee OA; they did not explore the effect of PEMF on QOL.[20,21] One explanation for the discordant results could be due to the inclusion of multiple therapies other than PEMF, including pulsed electrical stimulation and pulsed shortwave. The mechanisms of PEMF, pulsed electrical stimulation, and pulsed shortwave are different. Pulsed electrical stimulation[22] is delivered through capacitive coupling relying on the direct application of an electrical field. Pulsed shortwave therapy[23] involves the delivery of high-frequency electromagnetic energy in an intermittent mode and produces thermal and nonthermal effects.

PEMF parameters including frequency, intensity, treatment period, waveform, and geometry of exposure need to be considered when using PEMF therapy.[24] Exposure to low frequency (0–300 Hz) PEMF is extensively used for the treatment of diverse diseases, including osteoporosis,[25] low back pain,[26] bone nonunion and delayed union,[27] and oncology.[28] Low-intensity magnetic field is usually defined as <100 mT.[29] A previous systematic review has further explored the effects of 4 or more weeks PEMF therapy use on symptoms and QOL[19] in people with OA, which showed a reduction in pain. Low-frequency (≤100 Hz) PEMF therapy has shown a beneficial effect on physical function in another systematic review.[20]

The primary aim of this study was to investigate the effects of PEMF therapy, compared with placebo, on pain, stiffness, physical function, and QOL in patients with OA. The secondary aim was to describe the effects of PEMF parameters on symptoms and QOL in patients with OA.

Methods

Data Sources and Searches

Our methods conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[30] and our study protocol has been published in the PROSPERO International Prospective Register of Systematic Reviews (CRD42018109786). The search strategy was defined using the Population, Intervention, Comparison and Outcome method: (P) patients with OA; (I) PEMF; (C) sham PEMF or other intervention(s); and (O) pain, stiffness, physical function, and/or QOL-related outcomes.

Two authors (X.Y. and W.Y.) independently searched for relevant titles in the following electronic databases: Cochrane Central Register of Controlled Trials (The Cochrane Library, 2019 issue 4), PubMed (1966 to April 2019), CINAHL (1982 to April 2019), EMBASE (1988 to April 2019), and PEDro (1929 to April 2019). Further, we manually searched reference lists of all relevant articles and searched 3 clinical trial registers (ClinicalTrials.gov; Current Controlled Trials; WHO International ClinicalTrials Registry Platform). An example of the search strategy used in PubMed is provided in the Supplementary Appendix.

Study Selection

Studies were included if they met the following inclusion criteria: (1) were randomized, placebo controlled trials published in English; (2) adults (≥18 years) with OA (self-reported or clinically diagnosed); (3) PEMF therapy (or in combination with usual care) was the primary treatment intervention; and (4) pain, stiffness, physical function, and/or QOL outcomes were assessed. The following were excluded: studies where the population had a primary diagnosis of rheumatoid arthritis or other musculoskeletal disorder (eg, gout, inflammatory arthritis), studies where participants had a history of OA-related surgery and/or injury, review articles, abstracts, conference reports, and book chapters.

Data Extraction and Quality Assessment

Two authors (X.Y. and W.Y.) independently extracted outcome data from eligible studies; this included pain (ie, visual analogue scale [VAS], the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain subscale), stiffness (ie, WOMAC stiffness subscale),

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physical function (ie, WOMAC function subscale, the Lequesne index), and QOL (ie, EuroQoL and 36-item short-form health survey [SF-36]). We also extracted details of type of study, participant characteristics, treatment protocol, follow-up time, and other relevant information.

Risk of bias was assessed by 2 researchers (X.Y. and W.Y.) using the "risk of bias" tool[31] in accordance with methods recommended by the Cochrane Collaboration. We assessed bias across 7 domains:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias

Studies were scored as low, unclear, or a high risk of bias. The Grade of Recommendations Assessment, Development, and Evaluation (GRADE) system[32] was used to evaluate the overall quality of the evidence. In cases of conflicting scores between the 2 reviewers (X.Y. and W.Y.), a third expert (C.H.) reviewed the text and made the final decision.

Data Synthesis and Analysis

Meta-analysis was performed using Review Manager (RevMan) software (The Cochrane Collaboration, version 5.3).[33] For continuous variables, the mean difference was calculated when the outcome was assessed using the same scale across all studies. Alternatively, standardized mean differences (SMD) were calculated when continuous outcomes were measured using different scales across studies. The results of meta-analysis were presented as forest plots.

We used I^2 test statistics for evaluating heterogeneity; the outcome of this statistic can be interpreted as the proportion of variation in the sample estimates that is due to study differences.[31] To test whether significant heterogeneity existed, we used the Chi^2 test of homogeneity. Heterogeneity was considered significant when the P value was $<.10$.[34] Where there was evidence of heterogeneity ($I^2 > 25\%$), random effects models were used.

We categorized treatment duration into <4 weeks and ≥4 weeks in accordance with previously reported methods.[19] The range of treatment durations identified through our systematic review was used to inform our categories.

A sensitivity analysis was performed, excluding data obtained from high intensity and frequency.

Role of the Funding Source

This research was supported by the National Natural Science Foundation of China, which played no role in the design, conduct, or reporting of this study.

Results

Our search returned 473 articles; 238 articles were removed due to duplication. Of the 235 remaining articles, 202 articles were excluded after title and abstract screening due to failing to meet the inclusion criteria. Following full paper review, 16 articles[35–50] remained. Only 15 articles[35–44,46–50] were included in meta-analysis (Fig. 1); 1 article[45] was excluded due to incomplete data (only medians were reported for the outcomes of interest).

The total population studied across the 16 studies was 1078, comprising 554 participants in the treatment group and 524 participants in the control group. The mean age of patients was 59.5 years. Treatment time varied from 10 days to 6 weeks. Two different treatment durations (<4 weeks and 4–6 weeks) were used in the subgroup analysis. The longest follow-up time was 12 weeks. Osteoarthritic sites studied included the knee (N = 14),[35–39, 41–45,47–50] ankle (N = 1),[35] hand (N = 2),[35,46] and cervical spine (N = 2).[36,40] Treatment intervention types included PEMF therapy[35–40,42,45,47–49] and PEMF therapy in combination with routine physiotherapy.[41,43,44,46,50] Control intervention types included sham PEMF therapy, routine physiotherapy combined with sham PEMF therapy, no treatment, and medical therapy (eg, analgesic use when needed). The characteristics of the included studies are listed in the Table.

The overall assessment of the methodological quality is presented in the Supplementary Figure. Of the 16 studies included in our systematic review, only 2 studies[40,49] were consistently classified as 'low risk of bias' across 6 of the 7 domains. Other studies (N = 14) were judged as 'unclear risk of bias' for at least 2 aspects or 'high risk of bias' for at least 1 aspect. The results of our GRADE quality assessment are presented in the Supplementary Table. Overall, the quality of the evidence included in the analysis was either low or very low.

Pain

Fifteen studies,[35–44,46–50] comprising a total study population of 985 participants, had data on pain as assessed using VAS and/or the WOMAC pain subscale (Fig. 2). The overall inverse variance pooled SMD for VAS and the WOMAC pain subscale combined was 1.06 (95% CI = 0.61 to 1.51, $P < .00001$) in favor of PEMF with evidence of statistically significant heterogeneity ($I^2 = 90\%$, $P < .00001$). Eight studies,[37,40–44,46,48] comprising a total study population of 505 participants, with a duration of treatment shorter than 4 weeks showed a statistically significant beneficial effect of PEMF therapy for relieving pain. The pooled SMD for VAS and the WOMAC pain

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Table.
Characteristics of Included Studies in the Meta-Analysis

Study	Participant Characteristics	Protocol for Intervention Group					Protocol for Control Group	Outcome Measurement		Follow-up
		Type of Intervention	PEMF Waveforms	PEMF Intensity	PEMF Frequency	Duration of Rehabilitation		Statistically Significant Effect ($P < .05$)	No Statistically Significant Effect ($P > .05$)	
Trock et al, 1993[35]	27 individuals with OA (5 hand, 1 ankle, and 21 knee), (15 intervention, 12 control); age: at least 18 y	PEMF	N/A	10–20 Gauss	<30 Hz	18 half-hour periods of exposure over about 1 mo	Sham devices	Global pain, difficulty with ADL, pain performing ADL, worst discomfort in past week, pain on motion, and tenderness (VAS): ↓ Physician's global assessment: ↑		2 mo
Trock et al, 1994[36]	86 with knee OA and 81 cervical OA (86 intervention, 86 control), 69.8% female; mean age: 67.5 y	PEMF	Quasi-rectangular wave	10–15, 15–25, and 15–25 Gauss	5, 10, and 12 Hz	30 min, 3–5 times/wk, total 18 sessions over about 1 mo	Sham devices	Global pain, pain on motion, and tenderness (VAS): ↓ Physician's global assessment: ↑ Participant's overall assessment: ↑		1 mo
Jacobson et al, 2001[37]	176 with knee osteoarthritis (101 intervention, 75 control)	PEMF	Sinusoidal wave	2.74×10^{-7} G 2×10^{-7} G 1.5×10^{-7} G 1.26×10^{-7} G 9×10^{-8} G 7.8×10^{-8} G 5×10^{-8} G 3.4×10^{-8} G	7.7 Hz 5.6 Hz 4.1 Hz 3.5 Hz 2.5 Hz 2.1 Hz 1.4 Hz 0.976 Hz	6 min/session, 8 sessions/time, 8 times, 2 wk	Switched-off PEMF	Pain (VAS): ↓		2 & 4 wk
Pipitone et al, 2001[38]	75 with knee OA (39 intervention, 36 control), 27.5% female; mean age: 63 y; mean disease duration: 6 y	PEMF	N/A	<0.5 Gauss	3 Hz 7.8 Hz 20 Hz	10 min, 3 times/d, 6 wk	Sham devices	Physical function (WOMAC global and disablity scores): ↓ General health status (EuroQoL): ↑	Pain (4-point Likert scale, WOMAC pain score) Morning stiffness (WOMAC stiffness score) Physical function (Lequesne Index) General health status (SF-36)	2, 4, & 6 wk

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Table.
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Study	Participant Characteristics	Protocol for Intervention Group					Protocol for Control Group	Outcome Measurement		Follow-up
		Type of Intervention	PEMF Waveforms	PEMF Intensity	PEMF Frequency	Duration of Rehabilitation		Statistically Significant Effect ($P < .05$)	No Statistically Significant Effect ($P > .05$)	
Thamsborg et al, 2005[39]	90 with knee OA (45 intervention, 45 control), 54.2% female; mean age: 60 y; mean disease duration: 7.7 y	PEMF	Asymmetric wave	1 V/m	50 Hz	2 h/d, 5 d/wk, 6 wk	Sham devices	Pain (WOMAC pain score): ↓ Morning stiffness (WOMAC stiffness score): ↓ Physical function (WOMAC ADL Score): ↓	Bone structure (bone scintigraphic examinations)	2, 6, & 12 wk
Sutbeyaz et al, 2006[40]	32 with cervical OA (17 intervention, 15 control), 66% females; mean age: 42.5 y; disease duration: >3 mo	PEMF	N/A	40 μT	0.1–64 Hz	30 min/session, 2 sessions/d, 3 wk	Sham devices	Pain (VAS): ↓ Physical function and related disability (NPDS): ↓ Range of motion (chin-manibrium distance, occiput-C7 PS distance): ↓ Paravertebral muscle spasm (physician with manual pressure): ↓		3 wk
Ay et al, 2009[41]	55 with knee OA (30 intervention, 25 control), 72% females; mean age: 58 y, mean disease duration: 43 mo	Hot-pack+ TENS+ PEMF	N/A	105 μT	50 Hz	30 min/d, 15 sessions, 3 wk	Hot-pack+ TENS+ switched-off PEMF		Pain (VAS, Likert scores), Physical function (Lequesne index)	3 wk
Külcü et al, 2009[42]	45 with knee OA (15 PEMF intervention, 15 US intervention, 15 control), 77.8% females; mean age: 63.5 y, disease duration: at least 3 mo	PEMF	N/A	2–10 mT	2, 100, and 25 Hz	35 min/session, 5 sessions/wk, 3 wk	No treatment, paracetamol when needed	Pain (VAS, WOMAC pain score): ↓ Physical function (WOMAC function score): ↓ Joint stiffness (WOMAC stiffness score): ↓		3 wk

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Study	Participant Characteristics	Protocol for Intervention Group					Protocol for Control Group	Outcome Measurement		Follow-up
		Type of Intervention	PEMF Waveforms	PEMF Intensity	PEMF Frequency	Duration of Rehabilitation		Statistically Significant Effect ($P < .05$)	No Statistically Significant Effect ($P > .05$)	
Ozguclu et al, 2010[43]	40 with knee OA (20 intervention, 20 control), 72.5% females; mean age: 61.3 y, mean disease duration: 28 mo	Hot packs+US+PEMF	N/A	30 Gauss	50 Hz	30 min/d, 10 sessions, 2 wk	Hot packs+US+sham PEMF with near-zero intensity		Pain (VAS, WOMAC pain score) Physical function (WOMAC disability score) Morning stiffness (WOMAC stiffness score)	2 wk
Moldovan et al, 2012[44]	65 with knee OA (32 intervention, 33 control), 72.3% females; mean age: 57.8 y, mean disease duration: 3.85 y	Local US+local peloidotherapy +focalized PEMF	Triangular current shape	30 mT	1.5 Hz	15 min/d, 10 d	Local US+local peloidotherapy+ continuous magnetic field similar in intensity to magnetic field of Earth	Pain (VAS, WOMAC pain score): ↓ (excluding patients with radiological degree on Kellgren-Lawrence scale of 3 and 4 from both groups)	Pain (VAS, WOMAC pain score) Physical function (WOMAC global and physical activity scores) Morning stiffness (WOMAC stiffness score)	10 d
Pavlovic et al, 2012[45]	60 with knee OA (20 PEMF, 20 interfererence currents, 20 medicamentous therapy), 66.7% females; mean age: 53 y	PEMF	N/A	10 mT	50 Hz	30 min/d, 10 d	Interfererence currents; medicamentous therapy	Pain (Lattinen test score): ↓		10 d
Kanat et al, 2013[46]	50 with hand OA (25 intervention, 25 control), 100% females; mean age: 63 y, mean disease duration: 4.66 y	PEMF+ active range of motion/ strengthening exercises for hand	N/A	5–80 Gauss	25 Hz	20 min/d, 10 d	Sham PEMF+ same-hand exercises	Pain (SF-36 pain, VAS at rest, at motion): ↓ Joint stiffness (VAS): ↓ QOL (SF-36 general health): ↑ Function (SF-36 social function and vitality, Duruöz hand OA index, AUSCAN hand OA index): ↓	Function (SF-36 physical function, physical role limitations, mental health, & emotional role limitations) strength (hand grip strength, right and left; pinch grip strength, right and left)	10 d & 1 mo

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Table.
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Study	Participant Characteristics	Protocol for Intervention Group					Protocol for Control Group	Outcome Measurement		Follow-up
		Type of Intervention	PEMF Waveforms	PEMF Intensity	PEMF Frequency	Duration of Rehabilitation		Statistically Significant Effect ($P < .05$)	No Statistically Significant Effect ($P > .05$)	
Nelson et al, 2013[47]	34 with knee OA (15 intervention, 19 control), 70.6% females; mean age: 57 y, disease duration: at least 3 mo	PEMF	Sinusoidal wave	34 ± 8 V/m, at least 1000-fold below ambient magnetic field	6.8 MHz	15 min, 2 times/d, 6 wk	Sham devices	Pain (VAS): ↓		3, 14, 29, & 42 d
Wuschech et al, 2015[48]	57 with knee OA (44 intervention, 13 control), 35.1% females; mean age: 61.1 y	PEMF	Sinusoidal wave	105 mT	4–12 Hz	5 min, 2 times/d, 18 d	Sham devices	Pain (WOMAC pain score): ↓ Physical function (WOMAC global and disability scores): ↓ Morning stiffness (WOMAC stiffness score): ↓ Patient assessment of "effectiveness": ↑	Patient assessment of "tolerance"	18 d
Bagnato et al, 2016[49]	60 with knee OA (30 intervention, 30 control), 71.7% females; mean age: 67.7 y, mean disease duration: 12.1 y	PEMF	N/A	0.0098 W/103 cm^2	1000 Hz	12 h/d, 1 mo	Sham devices	Pain (VAS, WOMAC pain score): ↓ Physical function (WOMAC total and function scores): ↓ Morning stiffness (WOMAC stiffness score): ↓ Pain tolerance (distal interphalangeal pressure pain threshold, quadriceps femoris pressure pain threshold):↑ QOL (SF-36 v2, physical health): ↑	QOL (SF-36 v2, mental health)	1 mo
Dundar et al, 2016[50]	40 with knee OA (20 intervention, 20 control), 72.5% females; mean age: 57.2 y	PEMF+hot pack+ US+ TENS+ isometric knee exercise	N/A	100 μT	50 Hz	20 min/session, 5 sessions/wk, 4 wk	Sham PEMF+hot pack+US+ TENS+ isometric knee exercise		Pain (VAS) Physical function (WOMAC total score) Serum YKL-40 level	4 wk

[a]ADL = activities of daily living; N/A = not applicable; NPDS = neck pain and disability scale; OA = osteoarthritis; PEMF = pulsed electromagnetic field; QOL = quality of life; SF-36 = 36-item short-form health survey; TENS = transcutaneous electrical nerve stimulation; US = ultrasound; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

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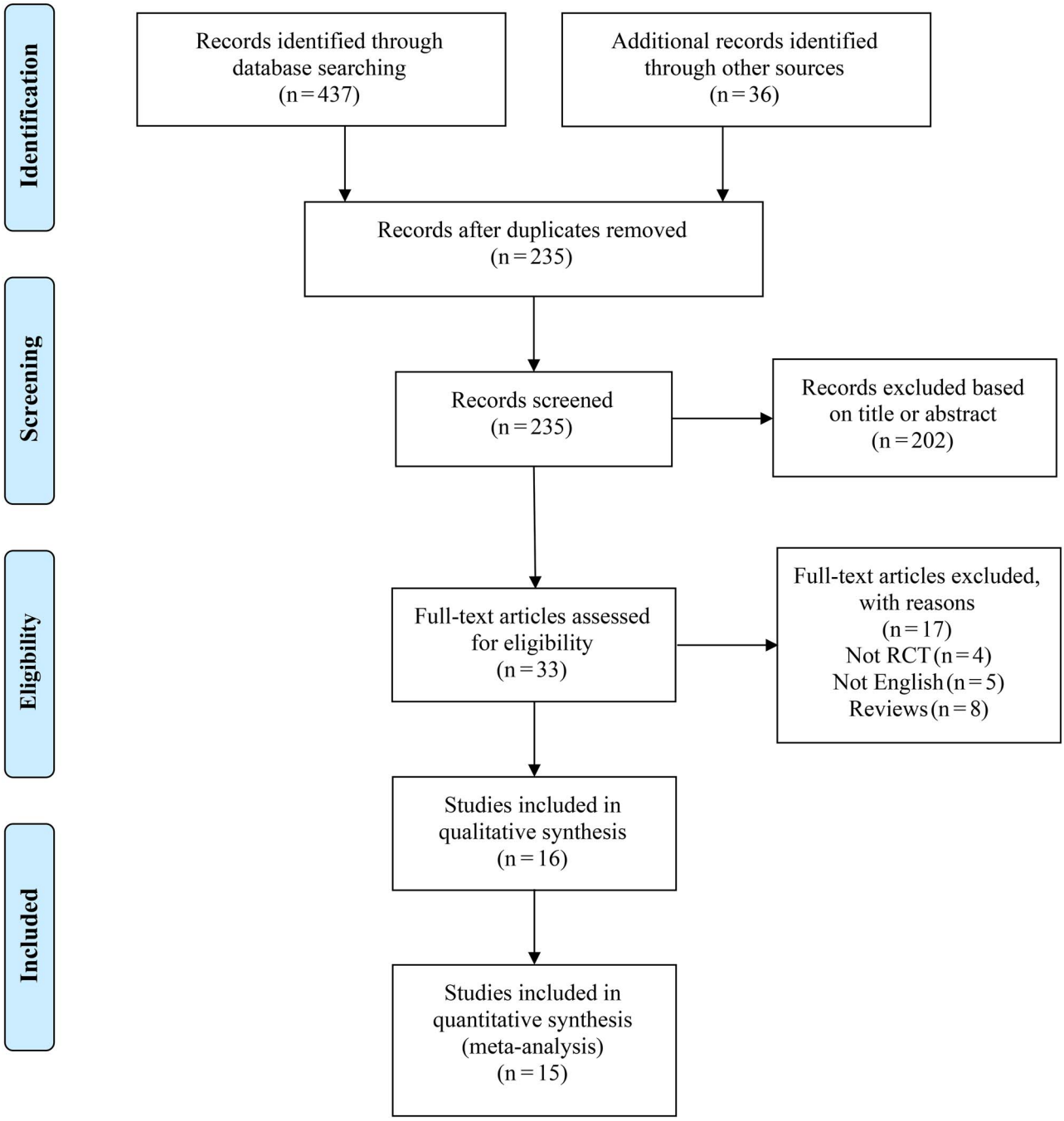

Figure 1.
Study flow diagram. RCT = randomized controlled trial.

subscale combined was 1.13 (95% CI = 0.44 to 1.83, P = .001) with evidence of statistically significant heterogeneity (I^2 = 91%, P < .00001). Seven studies,[35,36,38,39,47,49,50] comprising a total study population of 480 participants, assessed the effects of PEMF therapy on pain for 4 and 6 weeks. The pooled SMD for VAS and WOMAC pain subscale combined was 1.00 (95% CI = 0.38 to 1.63, P = .002) in favor of the significant beneficial effects of PEMF therapy; with statistically significant heterogeneity (I^2 = 90%, P < .00001). No statistically significant changes in heterogeneity and overall effect were observed in the sensitivity analysis in which we

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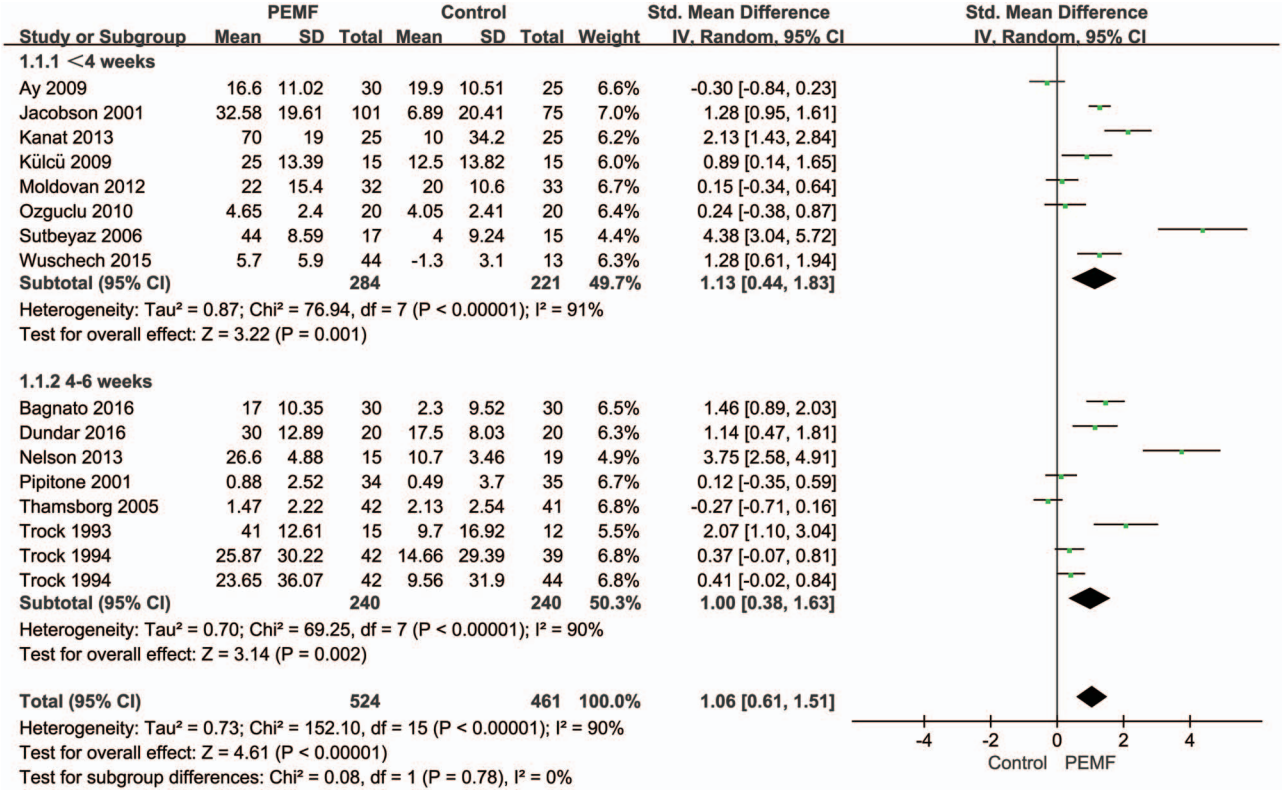

Figure 2.
Forest plot analysis of the effects of PEMF therapy on pain (WOMAC pain subscale and VAS) compared with control.

stratified by intensity and frequency of PEMF therapy (high intensity [105 mT][48] and high frequency [1000 Hz, 6.8 MHz][47,49]).

Stiffness

Seven studies[38,39,42–44,48,49] (total study population, N = 404) assessed joint stiffness using the WOMAC stiffness subscale (Fig. 3). The overall inverse variance pooled SMD was 0.37 (95% CI = 0.07 to 0.67, $P = .02$) in favor of PEMF with evidence of statistically significant heterogeneity ($I^2 = 53\%$, $P = .05$). Studies of <4 weeks PEMF therapy (study population, N = 192) (SMD = 0.40, 95% CI = −0.10 to 0.89, $P = .12$) and 4 to 6 weeks PEMF therapy (study population, N = 212) (SMD = 0.36, 95% CI = −0.08 to 0.79, $P = .11$) showed no evidence of a statistically significant difference in stiffness after PEMF therapy compared with the control group, respectively. Heterogeneity was statistically significant for studies of both <4 weeks ($I^2 = 61\%$, $P = .05$) and 4 to 6 weeks ($I^2 = 60\%$, $P = .08$). In sensitivity analysis, the overall inverse variance pooled SMD was 0.28 (95% CI = −0.02 to 0.57, $P = .07$) in favor of PEMF therapy without evidence of statistically significant heterogeneity ($I^2 = 42\%$, $P = .12$) when we excluded 1 article[49] with high-frequency (1000 Hz) PEMF therapy.

Physical Function

Eight studies[38,39,41–44,48,49] comprising a total of 457 participants assessed physical function using the Lequesne index or WOMAC function subscale (Fig. 4). Overall inverse variance pooled SMD for the Lequesne index and WOMAC function subscale combined was 0.46 (95% CI = 0.14 to 0.78, $P = .005$) in favor of PEMF; there was evidence of statistically significant heterogeneity ($I^2 = 63\%$, $P = .009$). Five studies,[41–44, 48] including 245 participants, of <4 weeks of PEMF therapy duration showed no significant differences in physical function compared with the control group. The pooled SMD for the Lequesne index and WOMAC function subscale combined was 0.55 (95% CI = −0.03 to 1.13, $P = .06$) with an I^2 value of 77% ($P = .001$). Three studies[38,39,49] including 212 participants assessed the effect of 4- to 6-week PEMF therapy on physical function. The pooled SMD for the WOMAC function subscale was 0.38 (95% CI = 0.11 to 0.65, $P = .006$) in favor of the PEMF without evidence of statistically significant heterogeneity ($I^2 = 0\%$, $P = .59$). No statistically significant changes in heterogeneity and overall effect were observed in the sensitivity analysis.

Quality of Life

Three studies[38,46,49] comprising a total study population of 179 participants assessed QOL using the EuroQoL or SF-36

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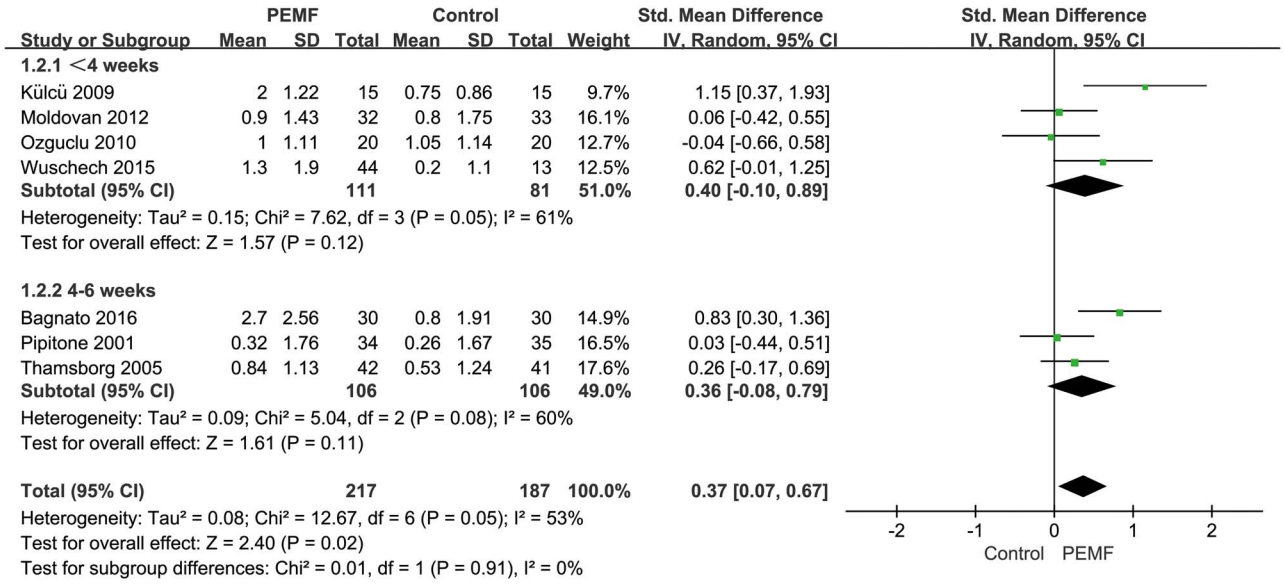

Figure 3.
Forest plot analysis of the effects of PEMF therapy on stiffness (WOMAC stiffness subscale) compared with control.

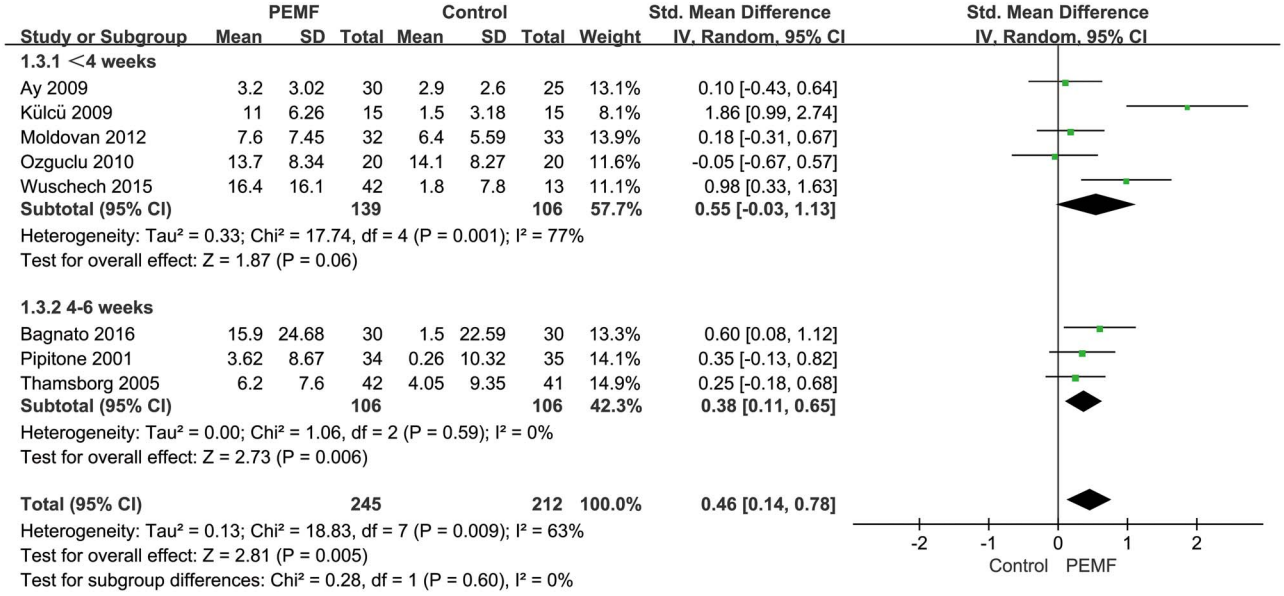

Figure 4.
Forest plot analysis of the effects of PEMF therapy on physical function (Lequesne index and WOMAC function subscale) compared with control.

scale (Fig. 5). The overall inverse variance pooled SMD for the EuroQoL and SF-36 scale combined was 1.49 (95% CI = −0.06 to 3.04, $P = .06$) with statistically significant heterogeneity ($I^2 = 95\%$, $P < .00001$). Only 1 study,[46] including 50 participants, of <4 weeks of PEMF therapy showed that there was statistically significant difference in QOL between PEMF and control groups (SMD = 3.62, 95% CI = 2.70 to 4.55, $P < .00001$). Two studies[38,49] including 129 participants assessed the effect of 4 to 6 weeks PEMF therapy on QOL. The pooled SMD for the EuroQoL and SF-36 scale combined was 0.49 (95% CI = 0.14 to 0.84, $P = .006$) in favor of the PEMF therapy; there was no evidence

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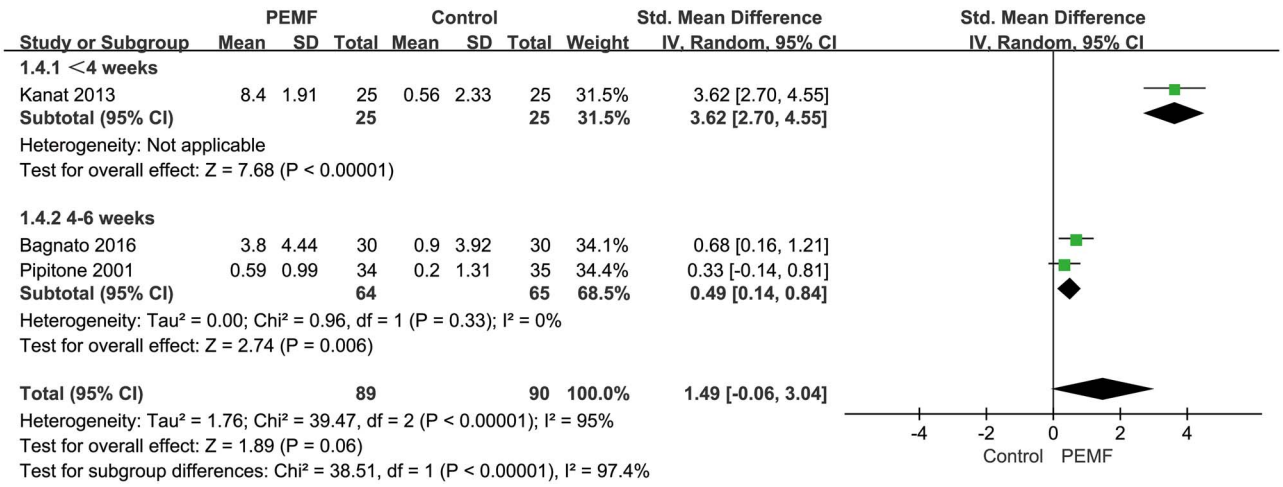

Figure 5.
Forest plot analysis of the effects of PEMF therapy on quality of life (EuroQoL and SF-36 scale) compared with control.

of statistically significant heterogeneity (I^2 = 0%, P = .33). No statistically significant changes in heterogeneity and overall effect were observed in the sensitivity analysis.

Discussion

Our study suggests that PEMF therapy, compared with placebo, has a beneficial effect on pain, stiffness, and physical function in patients with OA. Further, there was no observed association between PEMF therapy and QOL.

In our study, PEMF therapy was associated with a reduction in joint pain in those with OA compared with placebo. Our results are in keeping with the findings of a previous systematic review,[19] which found that PEMF therapy provided moderate pain relief in those with OA. Here, they only included studies of a duration ≥4 weeks, whereas in our study we also assessed studies of duration <4 weeks. Our study showed that PEMF therapy provided significant reductions in pain when used from 10 days to 6 weeks.

There is some evidence that at least 4 weeks of treatment are required based on biological plausibility.[19] We tested this theory by stratifying the included studies into these classes of treatment duration. There were no subgroup differences between the 2 treatment durations (<4 weeks and 4–6 weeks) for pain. Both <4 weeks and 4 to 6 weeks PEMF therapy showed a beneficial effect on pain. This would suggest that the duration of treatment may not be a critical factor in pain management. We further conducted a sensitivity analysis to describe the effects of high-intensity PEMF therapy (105 mT)[48] and high-frequency PEMF therapy (1000 Hz, 6.8 MHz)[47,49] on pain in those with OA. Our sensitivity analysis showed no statistically significant changes in levels of heterogeneity and overall effect on pain, thus confirming the stability of our results. PEMF device settings varied widely across studies; this may explain, in part, the high observed levels of heterogeneity.

In our study, a statistically significant improvement was observed for stiffness in patients with OA when using PEMF therapy, which was in contrast to the findings of a previous systematic review.[51] Here, the previous systematic review[51] included only 3 articles with stiffness data in those with knee OA, whereas in our study we included 7 articles with stiffness data in those with knee OA, which may have increased our ability to observe an association where one existed.

There was no evidence of statistically significant subgroup differences between 2 different treatment durations (<4 weeks and 4–6 weeks) for stiffness; data were available from 10 days to 6 weeks. In the subgroup analysis, no statistically significant improvement on stiffness was observed for <4 weeks and 4 to 6 weeks PEMF therapy for OA, which was in contrast to the findings of overall effect for stiffness. However, the direction of effects of <4 weeks (SMD = 0.4) and 4 to 6 weeks (SMD = 0.36) PEMF therapy was the same with overall effect for stiffness. The absence of statistical significance may be due to small study numbers of <4 weeks (N = 4) and 4 to 6 weeks (N = 3) for treatment duration. Our sensitivity analysis showed statistically significant changes in levels of heterogeneity and overall effect.

Our data suggest a beneficial effect of PEMF therapy on physical function in people with OA. In contrast to our findings, a previous systematic review[19] showed no statistically significant improvement on physical function. Here, the previous systematic review[19] included studies with both PEMF (N = 1) and pulsed electrical stimulation (N = 2) with evidence of statistically significant heterogeneity, whereas in our study we only included

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PEMF therapy, which may explain, in part, the conflicting results.

In our subgroup analysis, a statistically significant improvement on physical function was observed for 4 to 6 weeks' use of PEMF therapy for OA but not for <4 weeks use. These results considered together suggest that 4 to 6 weeks of use of PEMF therapy may be a potential treatment approach for improving physical function in those with OA. Our sensitivity analysis showed no statistically significant changes in levels of heterogeneity and overall effect, thus confirming the stability of our results.

We observed no association between PEMF therapy and QOL in people with OA, which was similar to the findings of a previous systematic review[19] (SMD of 0.09 [$P = .69$] and our study SMD of 1.49 [$P = .06$]). Data on QOL were available in only 3 studies, which may have limited our ability to detect an association between PEMF therapy and QOL. Three studies with 179 participants were included in our study; 2 studies with 139 participants were included in a previous systematic review.[19]

In our subgroup analysis, 1 study of 10 days[46] and 2 studies of 4 and 6 weeks[38,49] showed a positive effect of PEMF therapy on QOL in those with OA. Considering the subgroup difference, the duration of PEMF treatment might be the potential reason for heterogeneity in treatment effects of QOL. However, the subgroup difference might also be explained by different osteoarthritic sites. The study with <4 weeks PEMF therapy included patients with hand OA; 2 studies with 4- to 6-week PEMF therapy included patients with knee OA. Our sensitivity analysis showed no statistically significant changes in levels of heterogeneity and overall effect. Further studies are required to validate our findings.

To assess the clinical utility of a therapy, the amount of improvement that is important to patients must be determined.[52] Minimal clinically important difference (MCID), reflecting clinical significance,[53] is defined as the smallest difference in score in the domain of interest that patients perceive as beneficial.[54] The MCID can be standardized; they are traditionally presented as effect sizes of which the most commonly used are the standardized response mean and the SMD.[52,55] Angst et al suggested that the MCID, expressed as the SMD, for improvement on the WOMAC pain scale was 0.47.[53] Hence, the observed effects of PEMF therapy (SMD = 1.13 for <4 weeks, SMD = 1.00 for 4–6 weeks) on pain in our study were both statistically significant and clinically important. However, the effects of PEMF therapy on stiffness and physical function were not considered to be clinically significant based on existing thresholds. Angst et al suggested that the MCID, expressed as the SMD, for improvement in WOMAC stiffness subscale was 0.90 and for improvement in WOMAC function subscale was 0.93.[53] Therefore, the observed effects of PEMF therapy on stiffness (SMD = 0.37) and physical function (SMD = 0.46) in our study were only statistically significant but not clinically significant.

There were several strengths to our study. Firstly, while our primary aim was to explore the effects of PEMF therapy on symptoms and QOL, to our knowledge we are the first to examine the effect of PEMF parameters, including duration, frequency, and intensity, on symptoms and QOL. Secondly, we exclusively examined the effects of PEMF therapy on outcomes, whereas previous studies have examined PEMF, pulsed electrical stimulation, and pulsed shortwave. Further, our review compared the effect estimates with MICD to determine whether our results were clinically significant.

There are several potential limitations in our study. Firstly, high levels of heterogeneity across the outcome measures made harmonization difficult; however, in sensitivity analysis, we consistently observed a relationship between PEMF therapy and pain, physical function, and QOL, which would support the robustness of our findings. The main limitation to our study was small study numbers, particularly for sensitivity analysis when exploring the effects of different PEMF parameters. For instance, there were few data on high-intensity (N = 1) and -frequency (N = 2) PEMF therapy. In addition, the maximum PEMF treatment duration was 6 weeks and the longest follow-up time was 12 weeks across our included studies. Only short-term PEMF treatment effects were observed due to limited evidence, which limits the clinical relevance of the findings. Further, long-term follow-up studies are needed to explore the long-term effects of PEMF therapy. Further, we only included studies published in English; subsequently, relevant studies published in other languages may have been missed. Another potential limitation was that many of the included studies did not follow an intention-to-treat (ITT) analysis. There is evidence to suggest that trials that do not follow an ITT analysis show larger intervention effects than trials that do use an ITT analysis.[56] We consistently observed similar effect sizes in both the primary and sensitivity analyses, and the direction of effects was similar across our included studies, which would support the accuracy of our findings. Further, the magnitude of the associations was highly significant, which again would support the accuracy of our results.

In conclusion, this review suggests that PEMF therapy, compared with placebo, has clinically significant effects on joint pain in individuals with OA. Further, we observed a statistically significant beneficial effect of PEMF therapy on joint stiffness and physical function. We did not observe a relationship between PEMF parameters and symptoms. Our data suggest that the duration of treatment may not be a critical factor in pain management. However, the evidence was limited to short-term effects (up to

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3 months). Further studies are required to confirm the effects of PEMF therapy on QOL in patients with OA.

Author Contributions

Concept/idea/research design: X. Yang, H. He, T.A. Perry, C. He
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Data collection: X. Yang, W. Ye
Data analysis: X. Yang, H. He
Project management: H. He, T.A. Perry, C. He
Fund procurement: C. He
Providing facilities/equipment: C. He
Providing institutional liaisons: H. He, C. He
Consultation (including review of manuscript before submitting): X. Yang, T.A. Perry, H. He, W. Ye, C. He

T.A. Perry and C. He contributed equally to the work presented.

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Systematic Review Registration

This study protocol was published in the PROSPERO International Prospective Register of Systematic Reviews (CRD42018109786).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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