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Electrical stimulation for pain relief in knee osteoarthritis: systematic review and network meta-analysis

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SUMMARY

Objective: To investigate the efficacy of different electrical stimulation (ES) therapies in pain relief of patients with knee osteoarthritis (OA).

Method: Electronic databases including MEDLINE, Embase and Cochrane Library were searched through for randomized controlled trials (RCTs) comparing any ES therapies with control interventions (sham or blank) or with each other. Bayesian network meta-analysis was used to combine both the direct and indirect evidence on treatment effectiveness.

Results: 27 trials and six kinds of ES therapies, including high-frequency transcutaneous electrical nerve stimulation (h-TENS), low-frequency transcutaneous electrical nerve stimulation (l-TENS), neuromuscular electrical stimulation (NMES), interferential current (IFC), pulsed electrical stimulation (PES), and noninvasive interactive neurostimulation (NIN), were included. IFC is the only significantly effective treatment in terms of both pain intensity and change pain score at last follow-up time point when compared with the control group. Meanwhile, IFC showed the greatest probability of being the best option among the six treatment methods in pain relief. These estimates barely changed in sensitivity analysis. However, the evidence of heterogeneity and the limitation in sample size of some studies could be a potential threat to the validity of results.

Conclusion: IFC seems to be the most promising pain relief treatment for the management of knee OA. However, evidence was limited due to the heterogeneity and small number of included trials. Although the recommendation level of the other ES therapies is either uncertain (h-TENS) or not appropriate (l-TENS, NMES, PES and NIN) for pain relief, it is likely that none of the interventions is dangerous.

Level of evidence: LevelII, systematic review and network meta-analysis of RCTs.

Introduction

About 40% of the total population aged over 70 suffers from the most common form of arthritis-osteoarthritis (OA)[1]. In the USA, more than 9,000,000 people are affected by clinically and radiographically confirmed knee OA[2]. Knee OA is a widespread degenerative disease accompanied with great pain, the therapy options for which are plenty but no enough evidence to support them. Because pain is one of the most important causes for decline of life quality, the currently available treatments primarily aim to relieve joint pain for people with knee OA[3]. For the late-phase patients, so far the only effective therapy is to replace the knee joint. Combined with the increasing prevalence of knee OA[4], the rapid growth of knee replacement rate has drawn a high degree of attention to those effective nonsurgical treatments.

Electrical stimulation (ES) is a noninvasive treatment modality that involves various stimuli delivered superficially using electrodes placed on the skin[5]. It has been widely used in many fields, such as treatment, rehabilitation, and training purposes. There are different ES forms, including transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), interferential current (IFC), pulsed electrical stimulation (PES), noninvasive interactive neurostimulation (NIN), *etc.* Furthermore,

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TENS can be generally delivered at two different dosing, high-frequency (50–100 Hz) and low-frequency (2–10 Hz), the option of which is critical to effectiveness[6]. During the past few years, a rapidly growing interest has been observed in testing the treatment effects, but no consensus has been reached.

Although several systematic reviews and meta-analyses have been conducted to examine the effects of the three kinds of ES (including TENS, NMES and PES)[7–11], evidence was limited due to the lack of multiple comparisons of classical meta-analysis. Bayesian network meta-analysis is a method combining all available direct and indirect evidences on the relative treatment effects, enabling a unified, coherent analysis of all RCTs[12–15]. With the accumulation of recent evidence, this study performed a systematic review and network meta-analysis of randomized controlled trials (RCTs), which compared all six treatment regimens (high-frequency TENS (h-TENS), low-frequency TENS (l-TENS), NMES, IFC, PES and NIN) with the control group (sham or no intervention) for pain relief of patients with knee OA.

Materials and methods

Literature search

The electronic databases of Medline, Embase and Cochrane library were searched through using the combination of a series of logic keywords and text words related to OA, interventions of interest and RCT (Appendix 1). The most recent electronic search was conducted in February 2014. The reference lists of retrieved articles and reviews were identified. In addition, the following websites were searched through to retrieve unpublished and ongoing studies: Current Controlled Trials (http://www.controlled-trials.com/), ClinicalTrials.gov (http://www.clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/Default.aspx) were searched manually.

Study selection

Firstly, two researchers reviewed all the retrieved abstracts and full texts independently. If any disagreement was raised, it would be resolved by discussion and consultation with another researcher. Those papers meeting the following criteria were included in the analysis: (1) RCTs; (2) studies concerning patients with knee OA (3) studies containing at least two of the following eligible treatments: IFC stimulation, NMES, NINS, PES, TENS (high frequency or low frequency), and control group (blank or sham); (4) studies reporting the pain outcome of patients; (5) availability of full-text; (6) English language. Those trials whose additional modality (e.g., education or exercise) was unbalanced between the experimental group and the control group were excluded.

Quality assessment

Two researchers evaluated the methodological quality of the included studies separately. The modified oxford score[16,17], a scale ranged from 0 to 7 according to the descriptions of randomization, concealment allocation, blinding method and reporting of participant withdrawals, was used to measure the methodological quality of all studies.

Outcome measures

The primary goal of this study was to identify the effectiveness of pain management with different treatments of ES therapy. The measures of the relative treatment effect were the degree of pain intensity and the change pain score at last follow-up time point. As described by Jüni and colleagues[18], the highest score on the hierarchy of pain scale related outcomes was used if a study reported multiple pain scales. In order to standardize the pain outcomes of different studies, all pain scales were converted into a scale of 0–10 and the pain scores were recalculated[19]. Only data from the prior treatment at the last follow-up time point was extracted. For any study, if the standard deviation (SD) of outcome was not reported, it would be estimated according to the sample size, the standard error or the 95% confidence interval (95% CI) or on the basis of its figures. Moreover, the SDs of absolute changes were imputed from baseline in accordance with the details in the Cochrane Handbook[20] when they were not available in any individual trials. The correlation of $r = 0.8$ between the baseline and the last follow-up time point was used to estimate the SD for change from baseline. Lastly, the data of incidence rate of adverse effects was also extracted in order to evaluate the safety of interventions.

Statistical analysis

The random effect Bayesian network meta-analysis was used to compare the relative treatment effect of different treatments of knee OA. As a major advantage, network meta-analysis allows indirect comparisons of interventions among primary trials. In this study, the effect of pain management was expressed as the standard mean differences (SMD) among different treatment arms. A positive value represents a better pain relief effect and a negative value indicates less pain intensity after treatment.

The random effect Bayesian network meta-analysis was performed using WinBUGS software (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK), R version 3.0.2 (The R Foundation for Statistical Computing) and STATA software (version 11.0, StataCorp, College Station, TX). Network meta-analysis was considered to be the most comprehensive evidence on multiple treatment comparisons[15]. It combined direct comparisons within trials between two trials (such as A vs B) and indirect comparisons from trials which had one common treatment (such as A vs C using trials comparing A vs B and B vs C)[21]. The programming codes of random effect models for multi-arm trials are available at http://www.mtm.uoi.gr/ (Appendix 2). We used Markov Chains Monte Carlo method to obtain the pooled effect sizes. Three Markov chains run simultaneously with different initial values chosen arbitrarily. 50,000 times of simulation were generated for each of the three sets of initial values. The first 10,000 times of simulation were discarded due to the burn-in period. Pooled effect sizes were reported from the median of the posterior distribution, and the corresponding 95% credible intervals were applied using the 2.5th and 97.5th percentiles of the posterior distribution, which is similar to the conventional 95% CIs. In order to estimate the network inconsistency between indirect and direct estimates in each closed loop, the absolute difference between indirect and direct treatment effect estimates were calculated. Loops with the lower CI limit does not reach zero were considered as statistically significant inconsistency[22]. The fit of model to data was measured by calculating the posterior mean residual deviance. A model is considered fitting the data adequately when its mean of the residual deviance is similar to the number of data points[23].

A sensitivity analysis was conducted to examine the impact of low methodological quality and small sample size on the overall effect sizes. Meanwhile, in each Markov chain Monte Carlo cycle, each treatment is ranked according to the estimated effect size. These probabilities sum to one for each treatment and each rank. All treatments were ranked based on their effectiveness (first

best, second best, third best and so on) according to their posterior probabilities. Probability values were summarized and reported as the surface under the cumulative ranking (SUCRA)[24]. The value of SUCRA is ranged from 0 (worst treatment) to 1 (best treatment).

Classic pairwise meta-analysis was also performed to evaluate the heterogeneity across trials and the publication bias by using STATA software (version 11.0, StataCorp, College Station, TX). The heterogeneity was tested firstly by Q statistics ($P \leq 0.05$ was considered heterogeneous) and then by I^2 statistics, which measures the percentage of the total variation across studies ($I^2 \geq 50\%$ was considered heterogeneous). To evaluate the publication bias, Begg's tests were performed[25]. Comparison with a P value less than 0.05 would suggest the existence of publication bias.

Results

Study selection and characteristics

Figure 1 showed the selection process of included trials. A total of 1375 records were initially selected from database and website search. 926 records were identified after removing duplications. Then, 792 records were excluded with reasons and 134 full-texts trials were evaluated for eligibility. Finally, 27 studies[26–52] were included in this research. The details of the included studies are listed in Table I. The methodological quality assessment (Appendix 3) showed that there were eight low quality studies (score ≤ 3), ten medium quality studies (scored 4 or 5), and nine high quality studies (scored 6 or 7). Data from 20 studies[26–43,49,50] which include eight direct comparisons, and 995 patients with knee OA was available for network meta-analysis. Figure 2 presented the network structure of the analyzed comparisons for the primary outcomes. Results of the studies excluded by the network meta-analysis were reported in Appendix 4.

Pain intensity at last follow-up time point

The results of network meta-analysis about seven treatments (including the control group) comparing with each other were reported in Table II. IFC achieved a significantly lower pain intensity compared with the control group (SMD: −0.92, 95% CI: −1.72, −0.05), so does h-TENS (SMD: −0.78, 95% CI: −1.34, −0.22). No evidence of inconsistency between the direct and indirect estimates was observed in this network meta-analysis (Appendix 5). The evaluation of the goodness of fit for the models demonstrated adequate fit with a posterior mean residual deviance of 43.93 (43 data points). The probability distribution of each treatment was showed in Fig. 3. IFC got the highest probability (88%) and h-TENS got the second highest (74%) among all the seven treatments. Four direct comparisons showed significant evidence of heterogeneity (Appendix 6). There is no publication bias observed among studies except for the comparison between the high frequency of TENS and the control group ($P = 0.01$).

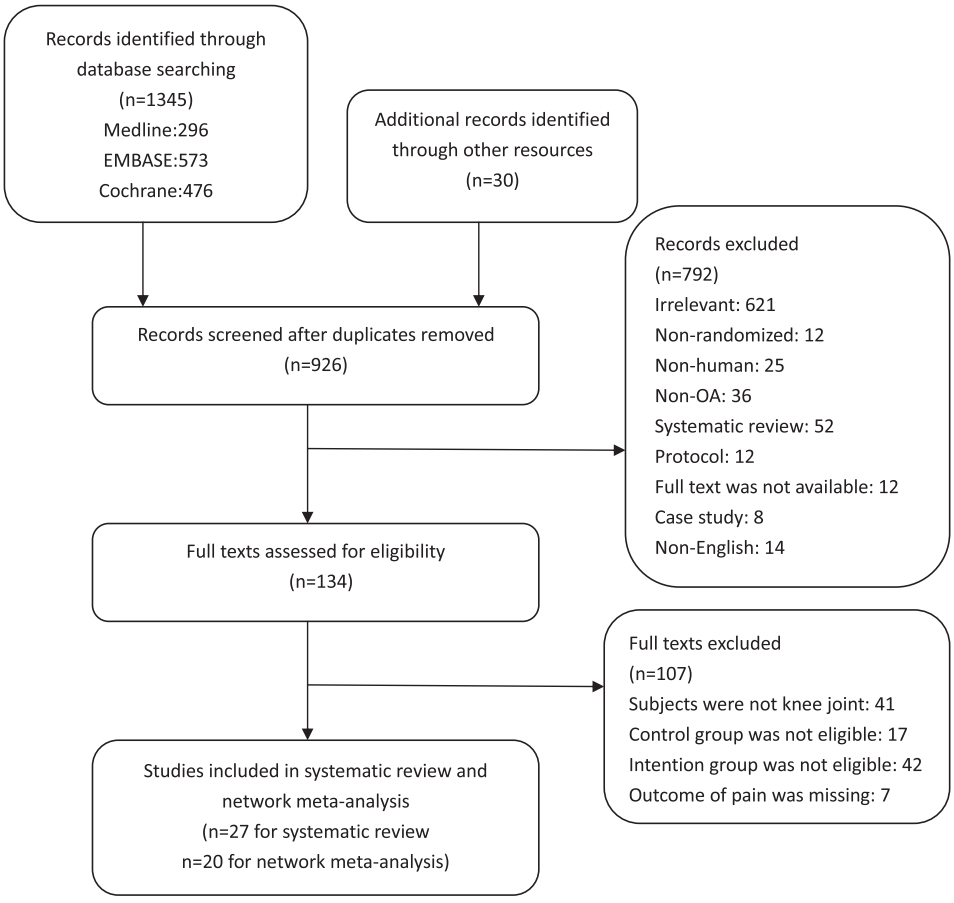

Fig. 1. Flowchart for the selection of included trials.

Table I
Characteristics of included studies

Study	Groups	Balance*	*N*	Age (years)	Gender (M/F)	Mean BMI	Parameters of intervention	Pain score	Test time‡
Itoh	G1: IFC	None	6	62–83†	11/21†	None	15 min, beat frequency: 122 Hz,	VAS, WOMAC	0, 1, 2, 3, 4, 5, 10 weeks
2008	G2: blank		6				feed frequency: 4 and 4.122 kHz		
Gundog	G1: 40 Hz IFC	None	15	59.6	3/12	28.1	20 min × 5 times × 3 weeks,	VAS, WOMAC	0, 1 month
2012	G2: 100 Hz IFC		15	59.6	3/12	29.5	strong but comfortable level		
	G3: 180 Hz IFC		15	60.2	3/12	28.7			
	G4: sham		15	60.5	3/12	28.8			
Elboim-Gabyzon	G1: NMES	Exercise	25	68.3	4/21	31.4	45 min × 12 times (within 8	VAS	1 week
2013	G2: blank		25	69.4	4/21	30.5	weeks), biphasic pulses, 75 Hz and 250 μs phase duration		
Palmieri-Smith	G1: NMES	None	16	58	Only females	32.7	3 times × 4 weeks, 50 Hz, duty	WOMAC	5, 16 weeks
2010	G2: blank		14	56.8		32.1	cycle ramp up 2 s, 10 s on-50 s off, intensity adjusted to at least 35% of MVC		
Gaines	G1: NMES	Education	20	70.8	3/17	31.5	15 min × 3 times × 12 weeks,	PPI, PRIT, AIMS2-PS	0, 4, 8, 12, 16 weeks
2012	G2: blank		18	70.9	5/13	31.6	50 Hz, rectangular waveform, pulsed, ramp up 3 s, 10 s on-50 s off, intensity for first 4 weeks at 10–20% MVC, weeks 5–8 20–30% MVC, weeks 9–12 30–40% MVC		
Talbot	G1: NMES	Education	18	70.1	3/15	29.5	15 min × 3 times × 4 weeks,	PRIT	0, 12 weeks
2003	G2: blank		16	70.8	4/12	31.6	50 Hz, rectangular waveform, pulsed, duty cycle 3 s ramp-up 1.5 ramp-down 10 s on–10 s off, intensity adjusted to 10–40% of MVC		
Mizusaki	G1: NMES	Exercise	44	60.6§	4/46§	30.1§	40 min × 2 times × 8 weeks,	WOMAC	8 weeks
2013	G2: blank		43	61.5§	10/40§	29.7§	50 Hz, rectangular waveform, pulsed, 10 s on–30 s off every 20 min		
Selfe	G1: NIN	None	18	70.1	5/13	29.3	20–30 min, weeks 1–3: 3	NRS, WOMAC, SF-36	1, 4, 8, 12 weeks
2008	G2: sham		19	70.0	7/12	31.7	times, weeks 4–6: 2 times, weeks 7–8: once a week		
Fary	G1: PES	None	34	70.7	17/17	29.4	Wear the device 7 h daily for 26	VAS, WOMAC	4, 16, 26 weeks
2011	G2: sham		36	68.9	20/16	26.8	weeks, pulsed, asymmetrically biphasic, exponentially decreasing waveform with 100 Hz and pulse width of 4 msec		
Garland	G1: PES	None	39	64.3	12/27	31.3	Wear the device for 6 h daily for	VAS, WOMAC	3 months
2007	G2: sham		19	69.9	8/11	30.2	12 weeks, 100 Hz, negative pulsed signal		
Vance	G1: l-TENS	None	25	55	11/14	36.2	40 to 50 min, low: 4 Hz; high:	VAS (rest, TUG, HTS)	None
2012	G2: h-TENS		25	57	9/16	33.6	100 Hz		
	G3: sham		25	57	9/16	39.2			
Pietrosimone	G1: h-TENS	Exercise	10	None	6/6§	28.6§	3 times × 4 weeks, 150 Hz	WOMAC	2, 4 weeks
2011	G2: sham		10		4/8§	29.5§			
	G3: blank		11		5/7§	28.6§			
Pietrosimone	G1: h-TENS	None	10	56	6/4	30.6	45 min, 15 Hz	VAS, WOMAC	20, 30, 45 min
2009	G2: blank		12	54	5/7	33.5			
Law	G1: l-TENS	None	13	82.7§	0/13	25	40 min × 5 times × 2 weeks,	VAS	None
2004	G2: h-TENS		12	84.3	0/12	24.8	low: 2 Hz; high: 100 Hz; mixed: an alternating frequency of 2 Hz and 100 Hz		
	G3: mixed TENS		13	80	1/12	26.4			
	G4: sham		10	83.2	0/10	29.2			
		None				None		VAS	0, 2 weeks

Cheing 2003	G1: h-TENS$_{20}$ G2: h-TENS$_{40}$ G3: h-TENS$_{60}$ G4: sham		10 10 10 8	69.2 63.2 63.5 66.1	1/9 1/9 1/9 1/7		20 min (TENS$_{20}$); 40 min (TENS$_{40}$); 60 min (TENS$_{60}$), 5 times × 2 weeks, 100 Hz		
Cheing 2002	G1: h-TENS G2: sham	None	16 16	65.3 64.1	2/14 1/15	None	60 min × 5 times × 4 weeks, 80 Hz	VAS	0, 4 weeks
Yurtkuran 1999	G1: l-TENS G2: sham	None	25 25	45–70 45–69	2/23 3/22	None	20 min × 5 times × 2 weeks, 4 Hz	PPI	0 week
Grimmer 1992	G1: h-TENS G2: burst TENS G3: sham	None	20§ 20 20	65.6 65.7 68.4	7/13 8/12 8/12	None	30 min, high: 80 Hz; burst: three Hz trains of seven 80 Hz pulses	VAS	0 week
Cetin 2008	G2: h-TENS G4: blank	Exercise, hot pack	20§ 20	61.9 61.1	Only females	29.5 27.7	3 times × 8 weeks, 20 min, 60–100 Hz	VAS	0 week
Atamaz 2012[α]	G1: h-TENS G2: IFC G3: sham	Exercise, education	29 27 67	61.9§ 62§ 61.6§	6/31§ 4/27§ 4/27§	28.4§ 29.8§ 28.5§	3 times × 3 weeks, TENS: 20 min, 80 Hz; IFC: 20 min, 100 Hz; CSW: 27.12 MHz, input 300 W, output 3.2 W	VAS, WOMAC	1, 3, 6 months
Rosemffet 2004	G1: FES G2: blank	Exercise	8 10	60†	6/20†	31.49 29.31	30 min × 3 times × 8 weeks, amplitude: 0.2 mlsg, 25-Hz, intensity: 60–80 V	WOMAC	0 week
Defrin 2005	G1: IFC1 G2: IFC2 G3: IFC3 G4: IFC4 G5: placebo G6: blank	None	11 11 12 11 9 8	68 70 68 68 73 64	None	None	20 min × 12 treatment sessions, total 4 weeks; intensity: 30% above (noxious stimulation) or 30% below (innocuous stimulation) the pain threshold; IFC1, noxious and unadjusted; IFC2, noxious and adjusted; IFC3, innocuous and unadjusted; IFC4, innocuous and adjusted	VAS	0 week
Zizic 1995	G1: PES G2: sham	None	30 22	None	None	None	Daily for 4 weeks; 100 Hz, 6.2 peak volts	VAS	4 weeks, 6 months
Ng 2003	G1: l-TENS G2: blank	Standard care and education	8 8	85.9 85.0	1/23†	None	20 min × 8 sessions, total 2 weeks; 2 Hz	NRS	0, 2 weeks
Adedoyin 2005	G1: h-TENS G2: IFC G3: blank	Exercises	15 16 15	55.4 53.2 56.87	5/10 5/11 8/7	30.3 25.99 26.85	20 min × 2 sessions × 4 weeks; TENS: 80 Hz, IFC: 80 Hz	VAS	1, 2, 3, 4 weeks
Simith 1983	G1: l-TENS G2: sham	None	15 15	65 70	5/10 5/10	None	20 min × 8 sessions, over 4 weeks; 5–10 Hz	Subjective linear scale	
Adedoyin 2002	G2: IFC G2: sham	Morning treatments and exercise	15 15	60.0 58.4	10/20†	27.65 28.80	20 min × 8 sessions, total 4 weeks. 100 Hz for first 15 min, 80 Hz for next 5 min	VAS	0 week

MVC, maximum voluntary contraction; PPI, present pain intensity; PRIT, Pain Rating Index-Total; AIMS2-PS, Arthritis Impact Measurement Scale 2-Pain Subscale; NRS, numeric rating scale; SF-36, Short Form-36; PSW, pulsed shortwave; W, watt; ms, microsecond; TUG, Time "up & Go" Test; HTS, heat temporal summation; N, number of subjects.

* Usual cares which were balance between groups.

† Only data for the whole trial is available.

‡ 0 means at the end of the treatment.

§ Only data from the baseline is available.

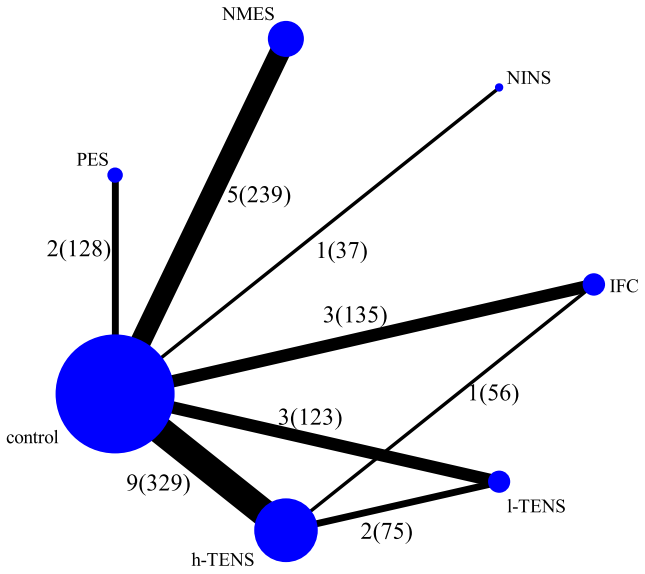

Fig. 2. Structure of network formed by interventions and their direct comparisons. The lines between treatment nodes indicate the direct comparisons made within randomized trials. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomly assigned participants (sample size). Numbers represents numbers of trials (number of analyzed patients) per comparison.

Change pain score at last follow-up time point

Table II showed the outcome of network meta-analysis in terms of change pain score at last follow-up time point. It indicated that only the IFC therapy is significantly more effective in pain relief compared to the control group (SMD: 2.06, 95% CI: 1.1–3.19). Meanwhile, IFC is also significantly more effective than NMES (SMD: 1.68, 95% CI: 0.36–3), h-TENS (SMD: 1.79, 95% CI: 0.66–3.04) and l-TENS (SMD: 1.81, 95% CI: 0.28–3.28) in pain relief. There is no evidence of inconsistency between the direct and indirect evidences (Appendix 5). The model provided an adequate fit to the data, with a posterior mean residual deviance of 45.04 (43 data points). Figure 4 shows the probability distribution of each treatment being ranked at each of the possible thirteen positions. According to the results of the posterior probability values of rank, it is found that the IFC therapy is most likely (98%) to be the best treatment among all treatments. There are significant evidence on the existence of heterogeneity among the six direct comparisons, and there is no publication bias observed among various studies (Appendix 6).

Sensitivity analysis

Sensitivity analysis was conducted after excluding the trials of low methodological quality and small sample size (sample size of an individual group < 15) in pain intensity at last follow-up time point. A total of 10 trials containing 640 patients were included in the sensitivity analysis. According to the results of pain intensity at last follow-up time point (Appendix 7), IFC again achieved significant lower pain intensity than the control group, as well as l-TENS. In addition, h-TENS achieved significantly lower pain intensity than l-TENS, but it is not significantly different from the control group. In terms of pain relief, the results were similar to the overall analysis, except that IFC achieved significantly better effect compared with PES.

Adverse effects

A total of seven trials reported adverse effects in their results. Three of them claimed no adverse effects related to the NMES, NINS and TENS treatment, respectively. Three other studies reported adverse effect of skin rash related to the PES treatment. However, there was no significant difference between the intervention and the control group in terms of the proportion of participants affected. One study reported that one patient in the NMES group exhibited blood pressure spike (Appendix 8).

Table II
network meta-analyses comparison between results of pain intensity (white) and change pain score (grey) at last follow-up time point, the data is presented as SMD and 95% credible intervals

IFC	-0.74 (-1.92,0.46)	-0.68 (-2.62,1.18)	-0.64 (-2.16,0.9)	-0.14 (-1,0.74)	-0.78 (-1.97,0.42)	-0.92 (-1.72,-0.05)
1.68 (0.36,3)	**NMES**	0.06 (-1.93,1.91)	0.1 (-1.29,1.51)	0.6 (-0.4,1.58)	-0.04 (-1.21,1.17)	-0.18 (-0.98,0.59)
1.63 (-0.8,4)	-0.05 (-2.38,2.21)	**NINS**	0.04 (-2.03,2.22)	0.54 (-1.2,2.29)	-0.1 (-2.04,1.84)	-0.24 (-1.92,1.49)
2.04 (-0.01,4.22)	0.36 (-1.78,2.53)	0.41 (-2.57,3.21)	**PES**	0.5 (-0.8,1.86)	-0.14 (-1.62,1.48)	-0.28 (-1.51,0.94)
1.79 (0.66,3.04)	0.1 (-0.93,1.12)	0.16 (-1.91,2.42)	-0.26 (-2.31,1.76)	**h-TENS**	-0.64 (-1.53,0.32)	-0.78 (-1.34,-0.22)
1.81 (0.28,3.28)	0.13 (-1.16,1.52)	0.18 (-2.01,2.47)	-0.23 (-2.59,1.96)	0.02 (-1.11,1.07)	**l-TENS**	-0.14 (-1.03,0.78)
2.06 (1.1,3.19)	0.38 (-0.49,1.24)	0.43 (-1.54,2.57)	0.02 (-2.03,1.8)	0.27 (-0.32,0.85)	0.25 (-0.77,1.38)	**Control**

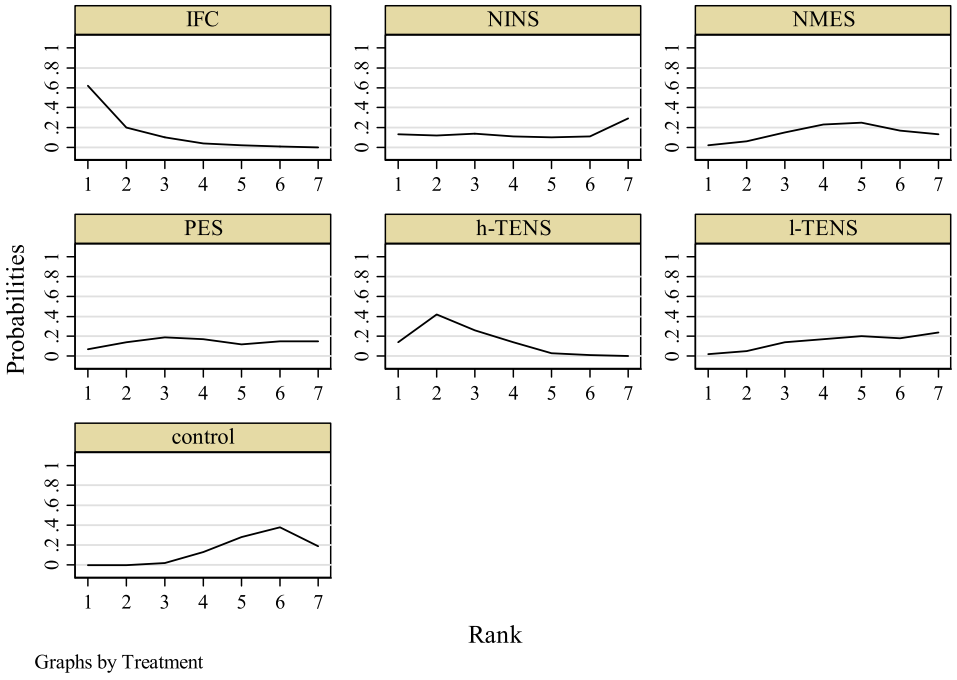

Fig. 3. Rankings for least pain intensity at last follow-up time point. Graph displays distribution of probabilities for each treatment. *X*-axis represents rank, *Y*-axis represents probabilities. Ranking indicates probability that treatments class is first "best," second "best," *etc.*

Discussion

This network meta-analysis reviewed six kinds of ES modalities (h-TENS, l-TENS, NMES, IFC, PES and NIN) in pain relief of patients with knee OA. The results showed that IFC is the only significantly effective treatment in terms of both pain intensity and change pain score at last follow-up time point when comparing with the control group (blank or sham). Meanwhile, IFC is most likely (highest probability) to be the best treatment option among the six treatment methods in pain relief. These findings barely changed in sensitivity analysis.

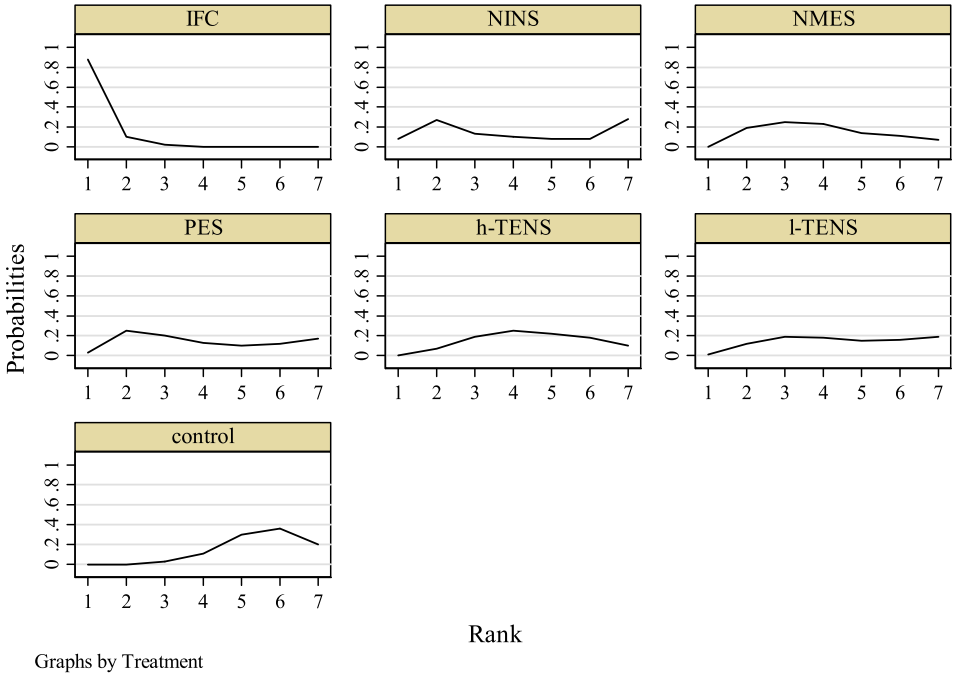

Fig. 4. Rankings for effectiveness of change pain score at last follow-up time point. *X*-axis represents rank, *Y*-axis represents probabilities. Graph displays distribution of probabilities for each treatment. Ranking indicates probability that treatments class is first "best," second "best," *etc.*

IFC, which delivers alternating medium-frequency current (4,000 Hz) through superficial electrodes placed on the skin, was developed in the early 1950s for diminishing skin impedance[53–55]. It possesses an added advantage of generating a parameter of amplitude-modulated frequency (AMF), which is a low-frequency current able to permeate more deeply and has been claimed as the main analgesic component of IFC[55,56]. Although IFC has been widely adopted throughout the world[57–60], a guidelines (2014)[61] developed by the Osteoarthritis Research Society International (OARSI) recently did not mention it as an effective therapy. A review published in 2013 covering almost all the rehabilitation interventions for OA suggested that IFC did not demonstrate benefits over the sham control[62], but the evidence was limited because it only included one RCT. Of note, a Cochrane systematic review conducted in 2009 observed very significant effects of IFC on pain relief[7], which was consistent with our results. Compare to the results of single pairwise classical meta-analysis, the findings of this study could be more useful in helping policy makers, service commissioners, and providers making choices among multiple ES therapies[63].

For the pain relief measurement, there are two commonly used options of network meta-analyses published in the British Medical Journal recently[19,64]. One calculated the change scores from baseline in case there were significant baseline differences caused by small sample size of the included studies[64]; the other one was based on pain intensity after treatment without clear explanation[19]. In addition, pain intensity decreases and change score differences might disagree. In view of such conditions, both of these two indices were used in this study to determine whether the results were consistent. As expected, part of the results were contradictory; for example, h-TENS achieved significantly lower pain intensity compared with the control group but did not perform better in terms of change pain score. Admittedly, except for the possibilities of significant baseline differences, like some other network meta-analysis[64], we estimated SD which was not reported in the original studies. This could partially explain the cause of inconsistency, deserving more attention for subsequent researches.

Similar to IFC, TENS is a form of electroanalgesia based on the gate control theory of pain perception[65], which delivers biphasic pulsed currents through two electrodes[66,67]. The previous systematic review and meta-analysis came to totally opposite conclusions: the meta-analysis showed a significant relief in knee OA pain (10), while the Cochrane systematic review did not[7]. Based on the Cochrane systematic review[7] and one RCT[68] in 2012, the recommendation level of TENS in the guidelines (2014)[61] developed by OARSI was uncertain for knee OA. Although the effect of pain relief was not consistent between pain intensity and change pain score at last follow-up time point, this study tends to suggest that h-TENS ranks the second in terms of the probability of being the best treatment option among the six methods, because half of the SD were estimated to calculate the overall change pain score and all of the baseline pain score differences between different groups were not significant. The other interventions (l-TENS, NMES, PES and NIN) failed to achieve better effects in pain relief when compared with the control group in terms of both indices.

Besides the effect of pain relief, the safety issue has also raised a lot of concerns. Similar to a systematic review and meta-analysis published in 2013[8], this study did not find any advantage of PES in pain relief when compared with the control group. However, it is clear that skin rash is associated with PES no matter in the PES group or in the sham group due to the use of conducting gel. Even though Fary *et al.* reported a much lower rate of adverse skin reaction when comparing biphasic current with monophasic current in healthy subjects[69], the RCT[34] conducted by Fary *et al.*, in 2011 only observed a slight decrease in skin rash in comparison with the two previous RCTs[35,48]. Fortunately, these incidences of skin rash were mild without occurrence of systemic reactions. So far, there is no obvious evidence showing that ES is unsafe except for some skin reactions in PES.

As far as we know, this is the first network meta-analysis of ES for knee OA, which integrated evidences from both direct and indirect comparisons for evaluating the relative effectiveness of pain relief. In this study, a comprehensive literature search with several databases and sources was performed to cover as many eligible trials as possible. Unlike some other network meta-analysis[70], the control group of this study was limited to sham or blank control, and the additional modality (e.g., education or exercise) was required to be balanced between groups in order to eliminate the potential impact of standard care. The differences between choosing pain intensity or change pain score to measure the effect of pain relief were also figured out in this study. This should be taken into account for further studies.

Nevertheless, the limitations of this study should not be ignored. Firstly, variations of treatment sessions, treating different doses of the same ES, and the different final follow-up time point might contribute to the significant evidence of heterogeneity. Although this study suggested that IFC seems to be the most promising pain relief treatment for the management of knee OA, evidence was limited due to the heterogeneity and small number of included trials. Fortunately, no obvious evidence of inconsistency was observed in this network meta-analysis. Secondly, the low level of methodological quality and the limitation in sample size of some studies could be a potential threat to the validity of results. However, the stability of the results of the sensitivity analyses confirms that the main findings of this research are robust and justified. Thirdly, this study only focused on the effectiveness of pain relief, without assessing the function improvement. The reason lies in the diversity of evaluation indices, which made it difficult to combine all indices together.

Conclusion

Our findings indicate that IFC seems to be the most promising pain relief treatment for the management of knee OA. However, evidence was limited due to the heterogeneity and small number of included trials. Although the recommendation level of the other ES therapies is either uncertain (h-TENS) or not appropriate (l-TENS, NMES, PES and NIN) for pain relief, it is likely that none of the interventions is dangerous.

Contribution of authors

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CZ and GL contributed to the study concept and design and drafted the manuscript. HL, TY and ZD contributed to data collection. YY and YZ contributed to preparation and data analysis. GL contributed to revision of the manuscript. All the authors contributed to the interpretation of the data and critically reviewed the manuscript for publication.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix 1. Search strategies for MEDLINE, The Cochrane Library and EMBASE database

Ovid/medline

1. osteoarthriti$.ti,ab,sh.
2. osteoarthro$.ti,ab,sh.
3. osteo?arthritic.ti,ab,sh.
4. gonarthriti$.ti,ab,sh.
5. gonarthro$.ti,ab,sh.
6. coxarthriti$.ti,ab,sh.
7. coxarthro$.ti,ab,sh.
8. arthros$.ti,ab.
9. arthrot$.ti,ab.
10. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.
11. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.
12. OR/1-11
13. exp electric stimulation therapy/
14. exp electric stimulation/
15. exp Electrical Stimulation Therapy/
16. iontophoresis.tw.
17. ((electric$ or electro$) adj (nerve or therapy)).tw.
18. ((electric$ or electro$) adj (stimulation or muscle)).tw.
19. ((electric$ or electro$) adj (function)).tw.
20. (high volt) or pulsed or electrostimulation or electroanalgezia.tw.
21. (ems or nes or nems or tens or tns or altens).tw.
22. neuromusc$ electric$.tw.
23. ((electric$ or electro$) adj25 current).tw.
24. ((electrical muscle stimulation) or (functional electrical stimulation) or (high voltage pulsed current) or (neuromuscular electrical stimulation) or (transcutaneous nerve stimulation)).tw.
25. OR/13-24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab,tw.
30. controlled.ti,ab.
31. randomly.ti,ab.
32. trial.ti,ab.
33. groups.ti,ab
34. ((randomized controlled trials) or (random$ allocation) or (double blind) or (single blind)).tw.
35. ((singl$ or doubl$ or tripl$) and (mask$ or blind$)).tw.
36. OR/26-35
37. 12 AND 25 AND 36

The Cochrane Library

#1. osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot*
#2. (knee* OR joint*) near/3 (pain* OR ach* OR discomfort*)
#3. (knee* OR joint*) near/3 stiff*
#4. MeSH descriptor Osteoarthritis explode all trees
#5. #1 or #2 or #3 or #4
#6. MeSH descriptor electric stimulation therapy explode all trees
#7. MeSH descriptor Neuromuscular Electrical Stimulation explode all trees
#8. MeSH descriptor Functional Electrical Stimulation explode all trees
#9. (electric* and (nerve or therapy or stimulation or muscle or function)):kw,ti,ab
#10. ((high volt) or pulsed or electrostimulation or electroanalgezia):kw,ti,ab
#11. (ems or nes or nems or tens or altens or ics):kw,ti,ab
#12. (electrical muscle stimulation) or (functional electrical stimulation) or (high voltage pulsed current) or (neuromuscular electrical stimulation) or (transcutaneous nerve stimulation)
#13. #6 or #7 or #8 or #9 or #10 or #11 or #12
#14. #5 and #13

Ovid/EMBASE

1. osteoarthriti$.ti,ab,sh.
2. osteoarthro$.ti,ab,sh.
3. osteo?arthritic.ti,ab,sh.
4. gonarthriti$.ti,ab,sh.
5. gonarthro$.ti,ab,sh.
6. coxarthriti$.ti,ab,sh.
7. coxarthro$.ti,ab,sh.
8. arthros$.ti,ab.
9. arthrot$.ti,ab.
10. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.
11. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.
12. OR/1-11
13. exp electric stimulation therapy/
14. exp electric stimulation/
15. exp Electrical Stimulation Therapy/
16. iontophoresis.tw.
17. ((electric$ or electro$) adj (nerve or therapy)).tw.
18. ((electric$ or electro$) adj (stimulation or muscle)).tw.
19. ((electric$ or electro$) adj (function)).tw.
20. (high volt) or pulsed or electrostimulation or electroanalgezia.tw.
21. (ems or nes or nems or tens or tns or altens).tw.
22. neuromusc$ electric$.tw.
23. ((electric$ or electro$) adj25 current).tw.
24. ((electrical muscle stimulation) or (functional electrical stimulation) or (high voltage pulsed current) or (neuromuscular electrical stimulation) or (transcutaneous nerve stimulation)).tw.
25. OR/13-24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab,tw.
30. controlled.ti,ab.
31. randomly.ti,ab.
32. trial.ti,ab.
33. groups.ti,ab.
34. ((randomized controlled trials) or (random$ allocation) or (double blind) or (single blind)).tw.
35. ((singl$ or doubl$ or tripl$) and (mask$ or blind$)).tw.
36. OR/26-35
37. 12 AND 25 AND 36

Appendix 2. WinBUGS codes of random effect models for multi-arm trials

```
model {
    for(i in 1:ns) {
        w[i,1]<- 0
        delta[i,t[i,1]]<- 0
        ss[i]<- sum(n[i,1:na[i]])
        nom[i]<- sum(nom1[i,1:na[i]])
        pooled.sd[i]<- sqrt(nom[i]/(ss[i]-na[i]))
        J[i]<- 1-(3/((4*(ss[i]-na[i]))-1))
#Normal Likelihood#
        for (k in 1:na[i]) {
            y[i,k] ~ dnorm(phi[i,t[i,k]],prec[i,k])
            se[i,k]<- sd[i,k]/sqrt(n[i,k])
            var[i,k]<- se[i,k]*se[i,k]
            prec[i,k]<- 1/var[i,k]
            nom1[i,k]<- (n[i,k]-1)*sd[i,k]*sd[i,k]
        }
#Parameterization of the model#
        phi[i,t[i,1]]<- u[i]*(pooled.sd[i]/J[i])
        for (k in 2:na[i]) {
            phi[i,t[i,k]]<- (u[i]+delta[i,t[i,k]])*(pooled.sd[i]/J[i])
            delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
            md[i,t[i,k]]<- d[t[i,k]] - d[t[i,1]]    + sw[i,k]
            taud[i,t[i,k]]<- tau *2*(k-1)/k
            w[i,k]<- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])
            sw[i,k]<- sum(w[i,1:k-1])/(k-1)
        }
    }
#Priors#
    SD ~ dnorm(0,1)I(0,1)
    tau<- 1/pow(SD,2)
    for(k in 1:(ref-1)) {
        d[k] ~ dnorm(0,.0001)
    }
    for(k in (ref+1):nt) {
        d[k] ~ dnorm(0,.0001)
    }
    for(i in 1:ns) {
        u[i] ~ dnorm(0,.0001)
    }
#Estimated & Predicted Standardized Mean Differences#
    d[ref]<- 0
    for (c in 1:(ref-1)) {
        SMD.ref[c]<- d[c] - d[ref]
        predSMD.ref[c] ~ dnorm( SMD.ref[c],tau)
    }
    for (c in (ref+1):nt) {
        SMD.ref[c]<- d[c] - d[ref]
        predSMD.ref[c] ~ dnorm( SMD.ref[c],tau)
    }
    for (c in 1:(nt-1)) {
        for (k in (c+1):nt) {
            SMD[c,k]<- d[c] - d[k]
            predSMD[c,k] ~ dnorm(SMD[c,k],tau)
        }
    }
#Ranking of treatments#
    for(k in 1:nt) {
        order[k]<-rank(d[],k)
# this is when the outcome is positive - omit   'nt+1-' when the outcome is negative
        most.effective[k]<-equals(order[k],1)
        for(j in 1:nt) {
            effectiveness[k,j]<- equals(order[k],j)
        }
    }
    for(k in 1:nt) {
        for(j in 1:nt) {
            cumeffectiveness[k,j]<- sum(effectiveness[k,1:j])
        }
    }
#SUCRAS#
    for(k in 1:nt) {
        SUCRA[k]<- sum(cumeffectiveness[k,1:(nt-1)]) /(nt-1)
    }
#Fit of the Model#
    for(i in 1:ns) {
        for(k in 1:na[i]) {
            Darm[i,k]<-(y[i,k]-phi[i,t[i,k]])*(y[i,k]-phi[i,t[i,k]])/var[i,k]
        }
        D[i]<- sum(Darm[i,1:na[i]])
    }
    D.bar<- sum(D[])
}
```

Appendix 3. Methodological quality assessment

Study	Randomized method	Concealment allocation	Blinding method	Follow-up	Total score
Itoh 2008	2	1	0	1	4
Gundog 2012	2	1	2	1	6
Elboim-Gabyzon 2013	2	2	2	1	7
Palmieri-Smith 2010	2	2	2	1	7
Gaines 2012	1	0	0	1	2
Talbot 2003	1	0	0	1	2
Mizusaki 2013	2	2	2	1	7
Selfe 2008	2	2	0	1	5
Fary 2011	2	2	2	1	7
Garland 2007	2	2	2	1	7
Vance 2012	2	2	2	1	7
Pietrosim-one 2011	1	2	2	1	6
Pietrosim-one 2009	1	2	2	1	6
Law 2004	2	0	2	1	5
Cheing 2003	1	0	0	1	2
Cheing 2002	1	0	1	1	3
Yurtkuran 1999	1	0	1	1	3
Grimmer 1992	2	0	2	1	5
Cetin 2008	1	0	2	1	4
Atamaz 2012	2	0	2	1	5
Rosemffet 2004	2	0	0	1	3
Defrin 2005	1	0	0	1	2
Zizic 1995	1	0	0	1	2
Ng 2003	2	0	2	1	5
Adedoyin 2005	1	0	2	1	4
Simith 1983	2	2	0	1	5
Adedoyin 2002	1	0	2	1	4

Appendix 5. Assessment of inconsistency

Loop	Pain intensity		Pain difference	
	Inconsistency	95% CI	Inconsistency	95% CI
IFC, h-TENS, control	0.263	(0.00, 1.88)	2.142	(0.00, 6.92)
h-TENS, l-TENS, control	0.260	(0.00, 2.68)	0.786	(0.00, 2.99)

Appendix 6. Results of heterogeneity and publication bias (Begg's test) according to pairwise meta-analysis

Comparison	Number of included studies	Pain intensity at last follow-up time point		Chang pain score at last follow-up time point	
		Heterogeneity (P/I^2)	Begg's test (P)	Heterogeneity (P/I^2)	Begg's test (P)
IFC vs control	3	0.00/93%	1.00	0.00/97%	0.30
IFC vs h-TENS	1	–	–	–	–
NMES vs control	5	0.04/61%	0.81	0.005/73%	0.46
NINS vs control	1	–	–	–	–
PES vs control	2	0.69/0%	1.00	0.04/76%	1.00
h-TENS vs control	9	0.00/72%	0.01	0.00/87%	0.47
h-TENS vs l-TENS	2	0.24/29%	1.00	0.05/74%	1.00
l-TENS vs control	3	0.00/93%	1.00	0.00/94%	1.00

Appendix 4. Results of the studies not included in the network meta-analysis

Study	Groups	Pain scale	Outcome of pain	
			Original data	Significance of difference
Rosemffet 2004	G1: FES G2: blank	WOMAC	Median (interquartile range) of pain intensity after treatment G1: 31.0 (22.7–48.8) G2: 25.0 (13.6–40.0)	NS
Defrin 2005	G1: IFC1(noxious, unadjusted) G2: IFC2(noxious, adjusted) G3: IFC3(innocuous, unadjusted) G4: IFC4(innocuous, adjusted) G5: sham G6: blank	VAS	Percent (%) pain relief from baseline G1: 53.6 G2: 64.1 G3: 50.0 G4: 43.2 G5: 14.5 G6: 0%	All active treatment groups comparing with sham, $P < 0.05$
Zizic 1995	G1: PES G2: sham	VAS	Percent (%) pain relief from baseline G1: 29.42 G2: 10.16	$P = 0.0365$
Ng 2003	G1: TENS G2: blank	NRS	Percent (%) pain relief from baseline G1: 15 G2: NR	NR
Adedoyin 2005	G1: h-TENS G2: IFC G3: blank	VAS	NR	NS
Simith 1983	G1: l-TENS G2: sham	Subjective linear scale (seven points)	Number (%) of patients who had pain relief G1: 7 (46%) G2: 4 (26.7)	NS
Jensen 1991	G1: h-TENS G2: l-TENS	Pain index	NR	NS
Adedoyin 2002	G2: IFC G2: sham	VAS	NR	$P < 0.01$

NS: not significant, NR: not report.

Appendix 7. Sensitivity analysis between results of pain intensity (white) and change pain score (grey) at last follow-up time point, the data is presented as SMD and 95% credible intervals

IFC	-1.06 (-2.55,0.59)	-1.2 (-3.12,0.7)	-1.13 (-2.68,0.29)	-1.05 (-2.26,0.15)	-2.46 (-4.14,-0.77)	-1.41 (-2.52,-0.42)
2.31 (0.33,4.29)	**NMES**	-0.14 (-2.05,1.81)	-0.06 (-1.7,1.49)	0.01 (-1.4,1.42)	-1.39 (-3.24,0.37)	-0.35 (-1.54,0.77)
2.4 (-0.08,4.8)	0.09 (-2.37,2.41)	**NINS**	0.08 (-1.82,2.05)	0.15 (-1.63,2)	-1.25 (-3.39,0.94)	-0.21 (-1.82,1.43)
2.42 (0.53,4.36)	0.11 (-1.8,2.19)	0.02 (-2.28,2.36)	**PES**	0.08 (-1.21,1.44)	-1.33 (-3.15,0.43)	-0.28 (-1.34,0.82)
2.54 (1.04,3.99)	0.23 (-1.43,2.01)	0.14 (-1.89,2.33)	0.12 (-1.62,1.81)	**h-TENS**	-1.41 (-2.79,-0.04)	-0.36 (-1.12,0.47)
3.55 (1.49,5.9)	1.23 (-0.93,3.43)	1.15 (-1.31,3.69)	1.13 (-1.22,3.37)	1 (-0.77,2.83)	**l-TENS**	1.05 (-0.3,2.44)
2.83 (1.47,4.18)	0.51 (-0.88,1.91)	0.43 (-1.46,2.35)	0.41 (-1.12,1.9)	0.28 (-0.7,1.26)	-0.72 (-2.58,1.06)	**Control**

Appendix 8. Details of adverse effects reported in including studies

Study	Intervention	Adverse effect	Number (%) in treatment group	Number (%) in control group
Fary 2011	PES	Skin rash	6 (18%)	6 (17%)
Garland 2007	PES	Skin rash	7 (17.9%)	4 (21.1%)
Zizic 1995	PES	Skin rash	7 (24%)	5 (21%)
Imoto 2013	NMES	Blood pressure spike	1 (0.02%)	0 (0%)

References

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965–73.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum 2008;58:26–35.
3. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis. Arthritis Rheum 1995;38:1535–40.
4. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, *et al*. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133:635–46.
5. Babault N, Cometti C, Maffiuletti NA, Deley G. Does electrical stimulation enhance post-exercise performance recovery? Eur J Appl Physiol 2011;111:2501–7.
6. Sato KL, Sanada LS, Rakel BA, Sluka KA. Increasing intensity of TENS prevents analgesic tolerance in rats. J Pain 2012;13:884–90.
7. Rutjes AW, Nüesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, *et al*. Transcutaneous electrostimulation for osteoarthritis of the knee. Cochrane Database Syst Rev 2009;4.
8. Negm A, Lorbergs A, MacIntyre NJ. Efficacy of low frequency pulsed subsensory threshold electrical stimulation vs placebo on pain and physical function in people with knee osteoarthritis: systematic review with meta-analysis. Osteoarthritis Cartilage 2013;21:1281–9.
9. Giggins OM, Fullen BM, Coughlan GF. Neuromuscular electrical stimulation in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil 2012;26:867–81.
10. Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-

analysis of randomised placebo-controlled trials. BMC Musculoskelet Disord 2007;8:51.
11. de Oliveira Melo M, Aragão FA, Vaz MA. Neuromuscular electrical stimulation for muscle strengthening in elderly with knee osteoarthritis–A systematic review. Complement Ther Clin Pract 2013;19:27–31.
12. Caldwell DM, Ades AE, Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331:897.
13. Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol 2010;63:875–82.
14. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002;21:2313–24.
15. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23:3105–24.
16. Elia N, Tramèr MR. Ketamine and postoperative pain–a quantitative systematic review of randomised trials. Pain 2005;113:61–70.
17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
18. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol 2006;20:721–40.
19. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, *et al*. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010;341.
20. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, http://www.cochrane-handbook.org; 2011.
21. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013;159:130–7.
22. Veroniki A, Salanti G. Graphical exploration of inconsistency in a network of randomized trials in R, http://www.mtm.uoi.gr/index.php/how-to-do-an-mtm/10-how-to-do-an-mtm/18-inconsistency; 2012.
23. Spiegelhalter DJ, Best NG. Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. Stat Med 2003;22:3687–709.
24. Salanti G, Ades AE, Ioannidis J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994:1088–101.
26. Itoh K, Hirota S, Katsumi Y, Ochi H, Kitakoji H. A pilot study on using acupuncture and transcutaneous electrical nerve stimulation (TENS) to treat knee osteoarthritis (OA). Chin Med 2008;3.
27. Gundog M, Atamaz F, Kanyilmaz S, Kirazli Y, Celepoglu G. Interferential current therapy in patients with knee osteoarthritis: comparison of the effectiveness of different amplitude-modulated frequencies. Am J Phys Med Rehabil 2012;91:107–13.
28. Elboim-Gabyzon M, Rozen N, Laufer Y. Does neuromuscular electrical stimulation enhance the effectiveness of an exercise programme in subjects with knee osteoarthritis? A randomized controlled trial. Clin Rehabil 2013;27:246–57.
29. Palmieri-Smith RM, Thomas AC, Karvonen-Gutierrez C, Sowers M. A clinical trial of neuromuscular electrical stimulation in improving quadriceps muscle strength and activation among women with mild and moderate osteoarthritis. Phys Ther 2010;90:1441–52.
30. Gaines JM, Metter EJ, Talbot LA. The effect of neuromuscular electrical stimulation on arthritis knee pain in older adults with osteoarthritis of the knee. Appl Nurs Res 2004;17:201–6.
31. Talbot LA, Gaines JM, Ling SM, Metter EJ. A home-based protocol of electrical muscle stimulation for quadriceps muscle strength in older adults with osteoarthritis of the knee. J Rheumatol 2003;30:1571–8.
32. Mizusaki Imoto A, Peccin S, Gomes da Silva KN, de Paiva Teixeira LE, Abrahão MI, Fernandes Moça Trevisani V. Effects of neuromuscular electrical stimulation combined with exercises versus an exercise program on the pain and the function in patients with knee osteoarthritis: a randomized controlled trial. Biomed Res Int 2013;2013:272018.
33. Selfe TK, Bourguignon C, Taylor AG. Effects of noninvasive interactive neurostimulation on symptoms of osteoarthritis of the knee: a randomized, sham-controlled pilot study. J Altern Complement Med 2008;14:1075–81.
34. Fary RE, Carroll GJ, Briffa TG, Briffa NK. The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: results of a double-blind, randomized, placebo-controlled, repeated-measures trial. Arthritis Rheum 2011;63:1333–42.
35. Garland D, Holt P, Harrington JT, Caldwell J, Zizic T, Cholewczynski J. A 3-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a highly optimized, capacitively coupled, pulsed electrical stimulator in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2007;15:630–7.
36. Vance CGT, Rakel BA, Blodgett NP, DeSantana JM, Amendola A, Zimmerman MB, *et al*. Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial. Phys Ther 2012;92:898–910.
37. Pietrosimone BG, Saliba SA, Hart JM, Hertel J, Kerrigan DC, Ingersoll CD. Effects of transcutaneous electrical nerve stimulation and therapeutic exercise on quadriceps activation in people with tibiofemoral osteoarthritis. J Orthop Sports Phys Ther 2011;41:4–12.
38. Pietrosimone BG, Hart JM, Saliba SA, Hertel J, Ingersoll CD. Immediate effects of transcutaneous electrical nerve stimulation and focal knee joint cooling on quadriceps activation. Med Sci Sports Exerc 2009;41:1175–81.
39. Law P, Cheing G. Optimal stimulation frequency of transcutaneous electrical nerve stimulation on people with knee osteoarthritis. J Rehabil Med 2004;36:220–5.
40. Cheing GL, Tsui AY, Lo SK, Hui-Chan CW. Optimal stimulation duration of tens in the management of osteoarthritic knee pain. J Rehabil Med 2003;35:62–8.
41. Cheing GL, Hui-Chan CW, Chan KM. Does four weeks of TENS and/or isometric exercise produce cumulative reduction of osteoarthritic knee pain? Clin Rehabil 2002;16:749–60.
42. Cetin N, Aytar A, Atalay A, Akman MN. Comparing hot pack, short-wave diathermy, ultrasound, and TENS on isokinetic strength, pain, and functional status of women with osteoarthritic knees: a single-blind, randomized, controlled trial. Am J Phys Med Rehabil 2008;87:443–51.
43. Atamaz FC, Durmaz B, Baydar M, Demircioglu OY, Iyiyapici A, Kuran B, *et al*. Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind,

randomized, controlled, multicenter study. Arch Phys Med Rehabil 2012;93:748–56.
44. Rosemffet MG, Schneeberger EE, Citera G, Sgobba ME, Laiz C, Schmulevich H, *et al*. Effects of functional electrostimulation on pain, muscular strength, and functional capacity in patients with osteoarthritis of the knee. J Clin Rheumatol 2004;10:246–9.
45. Defrin R, Ariel E, Peretz C. Segmental noxious versus innocuous electrical stimulation for chronic pain relief and the effect of fading sensation during treatment. Pain 2005;115:152–60.
46. Ng M, Leung MC, Poon D. The effects of electro-acupuncture and transcutaneous electrical nerve stimulation on patients with painful osteoarthritic knees: a randomized controlled trial with follow-up evaluation. J Altern Complement Med 2003;9:641–9.
47. Smith CR, Lewith GT, Machin D. TNS and osteo-arthritic pain. Preliminary study to establish a controlled method of assessing transcutaneous nerve stimulation as a treatment for the pain caused by osteo-arthritis of the knee. Physiotherapy 1983;69:266.
48. Zizic TM, Hoffman KC, Holt PA, Hungerford DS, O Dell JR, Jacobs MA, *et al*. The treatment of osteoarthritis of the knee with pulsed electrical stimulation. J Rheumatol 1995;22:1757–61.
49. Yurtkuran M, Kocagil T. TENS, electroacupuncture and ice massage: comparison of treatment for osteoarthritis of the knee. Am J Acupunct 1998;27:133–40.
50. Grimmer K. A controlled double blind study comparing the effects of strong burst mode TENS and high rate TENS on painful osteoarthritic knees. Aust J Physiother 1992;38:49–56.
51. Adedoyin RA, Olaogun MO, Oyeyemi AL. Transcutaneous electrical nerve stimulation and interferential current combined with exercise for the treatment of knee osteoarthritis: a randomised controlled trial. Hong Kong Physiotherapy J 2005;23:13–9.
52. Adedoyin RA, Olaogun MO, Fagbeja OO. Effect of interferential current stimulation in management of osteo-arthritic knee pain. Physiotherapy 2002;88:493–9.
53. Poitras S, Brosseau L. Evidence-informed management of chronic low back pain with transcutaneous electrical nerve stimulation, interferential current, electrical muscle stimulation, ultrasound, and thermotherapy. Spine J 2008;8:226–33.
54. Goats GC. Interferential current therapy. Br J Sports Med 1990;24:87.
55. Low J. Interferential current therapy. Br J Sports Med 1990;24:87.
56. Nikolova L. The hemodynamic disorders in Sudeck's atrophy and the effect on them of interference therapy. Vopr kurortol fizioter i lech fiz kult 1991:38–41.
57. Pope GD, Mockett SP, Wright JP. A survey of electrotherapeutic modalities: ownership and use in the NHS in England. Physiotherapy 1995;81:82–91.
58. Lindsay DM, Dearness J, McGinley CC. Electrotherapy usage trends in private physiotherapy practice in Alberta. Physiother Can 1994;47:30–4.
59. Cuskeüf G. A survey of electromodality usage in private physiotherapy practices. Physiotherapy 1990;36:249–56.
60. Robertson VJ, Spurritt D. Electrophysical agents: implications of their availability and use in undergraduate clinical placements. Physiotherapy 1998;84:335–44.
61. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, *et al*. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.
62. Davis AM, MacKay C. Osteoarthritis year in review: outcome of rehabilitation. Osteoarthritis Cartilage 2013;21:1414–24.
63. Cooper NJ, Kendrick D, Achana F, Dhiman P, He Z, Wynn P, *et al*. Network meta-analysis to evaluate the effectiveness of interventions to increase the uptake of smoke alarms. Epidemiol Rev 2012;34:32–45.
64. Uthman OA, van der Windt DA, Jordan JL, Dziedzic KS, Healey EL, Peat GM, *et al*. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013;347.
65. Melzack R, Wall PD. Pain mechanisms: a new theory. Surv Anesthesiol 1967;11:89–90.
66. Sjölund B, Eriksson M, Loeser J. Transcutaneous and implanted electric stimulation of peripheral nerves. Manag pain 1990;2:1852–61.
67. Low J. Transcutaneous and implanted electric stimulation of peripheral nerves. Manag pain 1990;2:1852–61.
68. Ulus Y, Tander B, Akyol Y, Durmus D, Buyukakıncak O, Gul U, *et al*. Therapeutic ultrasound versus sham ultrasound for the management of patients with knee osteoarthritis: a randomized double-blind controlled clinical study. Int J Rheum Dis 2012;15:197–206.
69. Fary RE, Briffa NK. Monophasic electrical stimulation produces high rates of adverse skin reactions in healthy subjects. Physiother Theory Pract 2011;27:246–51.
70. Corbett MS, Rice S, Madurasinghe V, Slack R, Fayter DA, Harden M, *et al*. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. Osteoarthritis Cartilage 2013;21:1290–8.