Transcutaneous electrostimulation for osteoarthritis of the knee (Review)

Rutjes AWS, Nüesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, Brosseau L, Reichenbach S, Jüni P

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[Intervention Review]

Transcutaneous electrostimulation for osteoarthritis of the knee

Anne WS Rutjes[1], Eveline Nüesch[1], Rebekka Sterchi[1], Leonid Kalichman[2], Erik Hendriks[3], Manathip Osiri[4], Lucie Brosseau[5], Stephan Reichenbach[6], Peter Jüni[1]

[1]Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Department of Physical Therapy, Recanati School for Community Health Professions, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel. [3]Epidemiology Department, Maastricht University, Maastricht, Netherlands. [4]Department of Medicine, Faculty of Medicine, Bangkok, Thailand. [5]School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa, Ottawa, Canada. [6]Department for Rheumatology, Clinical Immunology, and Allergology, University Hospital, Bern, Switzerland

Contact address: Anne WS Rutjes, Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, Bern, 3012, Switzerland. arutjes@ispm.unibe.ch. rutjes@negrisud.it. (Editorial group: Cochrane Musculoskeletal Group.)

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ABSTRACT

Background

Osteoarthritis is the most common form of joint disease and the leading cause of pain and physical disability in the elderly. Transcutaneous electrical nerve stimulation (TENS), interferential current stimulation and pulsed electrostimulation are used widely to control both acute and chronic pain arising from several conditions, but some policy makers regard efficacy evidence as insufficient.

Objectives

To compare transcutaneous electrostimulation with sham or no specific intervention in terms of effects on pain and withdrawals due to adverse events in patients with knee osteoarthritis.

Search strategy

We updated the search in CENTRAL, MEDLINE, EMBASE, CINAHL and PEDro up to 5 August 2008, checked conference proceedings and reference lists, and contacted authors.

Selection criteria

Randomised or quasi-randomised controlled trials that compared transcutaneously applied electrostimulation with a sham intervention or no intervention in patients with osteoarthritis of the knee.

Data collection and analysis

We extracted data using standardised forms and contacted investigators to obtain missing outcome information. Main outcomes were pain and withdrawals or dropouts due to adverse events. We calculated standardised mean differences (SMDs) for pain and relative

risks for safety outcomes and used inverse-variance random-effects meta-analysis. The analysis of pain was based on predicted estimates from meta-regression using the standard error as explanatory variable.

Main results

In this update we identified 14 additional trials resulting in the inclusion of 18 small trials in 813 patients. Eleven trials used TENS, four interferential current stimulation, one both TENS and interferential current stimulation, and two pulsed electrostimulation. The methodological quality and the quality of reporting was poor and a high degree of heterogeneity among the trials (I^2 = 80%) was revealed. The funnel plot for pain was asymmetrical (P < 0.001). The predicted SMD of pain intensity in trials as large as the largest trial was -0.07 (95% CI -0.46 to 0.32), corresponding to a difference in pain scores between electrostimulation and control of 0.2 cm on a 10 cm visual analogue scale. There was little evidence that SMDs differed on the type of electrostimulation (P = 0.94). The relative risk of being withdrawn or dropping out due to adverse events was 0.97 (95% CI 0.2 to 6.0).

Authors' conclusions

In this update, we could not confirm that transcutaneous electrostimulation is effective for pain relief. The current systematic review is inconclusive, hampered by the inclusion of only small trials of questionable quality. Appropriately designed trials of adequate power are warranted.

PLAIN LANGUAGE SUMMARY

Transcutaneous electrostimulation for osteoarthritis of the knee

This summary of a Cochrane review presents what we know from research about the effect of transcutaneous electrostimulation on osteoarthritis of the knee.

The review shows that in people with osteoarthritis:

- We are uncertain whether transcutaneous electrostimulation affects pain or your ability to use your knee because of the very low quality of the evidence.

- Transcutaneous electrostimulation may not have any side effects. We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects.

What is osteoarthritis and what is transcutaneous electrostimulation?

Osteoarthritis (OA) is a disease of the joints, such as your knee. When the joint loses cartilage, the bone grows to try and repair the damage. Instead of making things better, however, the bone grows abnormally and makes things worse. For example, the bone can become misshapen and make the joint painful and unstable. This can affect your physical function or ability to use your knee.

Transcutaneous electrostimulation, such as TENS, is a kind of pain relief typically using electrical currents applied to the skin. Transcutaneous electrostimulation machines are typically small, battery-operated machines with 2 electrodes attached. Electrodes are wires that send the electrical current. Usually, you connect two electrodes from the machine to your skin on the painful area. Your doctor or physiotherapist will show you how to use it, and most machines can be used at home.

Best estimate of what happens to people with osteoarthritis who use transcutaneous electrostimulation up to 4 weeks after using it:

Pain

- People who used electrostimulation had an improvement in their pain of about 2 on a scale from 0 (no pain) to 10 (extreme pain) 4 weeks after using it.

- People who used a fake electrostimulation machine or just took their usual treatments had an improvement in their pain of about 2 on a scale from 0 (no pain) to 10 (extreme pain) 4 weeks after using it.

- People had no more average improvement when using electrostimulation, and no more people responded to treatment with electrostimulation compared with people who used a fake electrostimulation machine or just took their usual treatments (difference of 0%).

Physical Function

- People who used electrostimulation had an improvement in their physical function of about 2 on a scale from 0 (no disability) to 10 (extreme disability) 4 weeks after using it.

- People who used a fake electrostimulation machine or just took their usual treatments had an improvement in their physical function of about 1 on a scale from 0 (no disability) to 10 (extreme disability) 4 weeks after using it.

- People using electrostimulation had 1 unit more improvement in their knee function when compared to people who used a fake electrostimulation machine or just took their usual treatments.

Another way of saying this is:

- 29 people out of 100 who used electrostimulation respond to treatment (29%).

- 26 people out of 100 who used a fake electrostimulation machine or just took their usual treatments respond to treatment (26%).

- 3 more people respond to treatment with electrostimulation compared with people who used a fake electrostimulation machine or just took their usual treatments (difference of 3%).

Dropouts or withdrawals from the trial because of side effects

- 2 people out of 100 who used electrostimulation dropped out or withdrew from the trial because of side effects (2%).

- 2 people out of 100 who used a fake electrostimulation machine or just took their usual treatments dropped out of the trial because of side effects (2%).

- There was no difference in the number of people who dropped out of the trial because of side effects (difference of 0%). This could be the result of chance.

Side effects

- 15 people out of 100 who used electrostimulation experienced side effects (15%).

- 15 people out of 100 who used a fake electrostimulation machine or just took their usual treatments experienced side effects (15%).

- There was no difference in the number of people who experience side effects (difference of 0%). This could be the result of chance.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Any type of transcutaneous electrostimulation compared with sham or no intervention for osteoarthritis of the knee

Patient or population: patients with osteoarthritis
Settings: physical therapy practice of outpatient clinic
Intervention: any type of transcutaneous applied electrostimulation
Comparison: sham or no specific intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk*	Corresponding risk				
	Sham or no specific intervention	Any type of transcutaneous electrostimulation				
Pain Various pain scales Median follow-up: 4 weeks	**-1.8 cm change** on 10 cm VAS[1] 29% improvement	**-2.0 cm change** (Δ -0.2 cm, -1.2 to 0.8 cm)[2] 33% improvement (Δ +4%, -13% to +20%)[3]	SMD -0.07 (-0.46 to 0.32)	726 (16 studies)	+000 very low[4]	Little evidence of beneficial effect (NNT: not statistically significant) The estimated pain in the intervention group of large trials was derived from meta-regression using the standard error as independent variable
Function Various validated function scales Median follow-up: 4 weeks	**-1.2 units on WOMAC** (range 0 to 10)[1] 21% improvement	**-2.3 units on WOMAC** (Δ -1.1, -1.6 to -0.6)[5] 41% improvement (Δ +20%, +11% to +29%)[6]	SMD -0.34 (-0.54 to -0.14)	407 (9 studies)	+000 very low[7]	NNT: 29 (95% CI 19 to 69)[8]
Number of patients experiencing any adverse event Median follow-up: 4 weeks	150 per 1000 patient-years[1]	153 per 1000 patient-years (80 to 296)	RR 1.02 (0.53 to 1.97)	175 (3 studies)	++00 low[9]	No evidence of harmful effect (NNH: not statistically significant)

Number of patients withdrawn or dropped out because of adverse events Median follow-up: 4 weeks	17 per 1000 patient-years[1]	16 per 1000 patient-years (3 to 102)	RR 0.97 (0.16 to 6.00)	363 (8 studies)	+++O moderate[10]	No evidence of harmful effect (NNH: not statistically significant)
Number of patients experiencing any serious adverse event Median follow -up: 4 weeks	4 per 1000 patient-years[1]	1 per 1000 patient-years (0 to 29)	RR 0.33 (0.02 to 7.32)	195 (4 studies)	++OO low[11]	No evidence of harmful effect (NNH: not statistically significant)

*The basis for the **assumed risk** in the safety outcomes (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; GRADE: GRADE Working Group grades of evidence (see explanations); NNT: number needed to treat; NNH: number needed to harm; RR: risk ratio; SMD: standardised mean difference

GRADE Working Group grades of evidence

High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality (+OOO): We are very uncertain about the estimate.

[1] Median reduction as observed across control groups in large osteoarthritis trials (Nuesch 2009).

[2] Standardised mean differences (SMDs) were back-transformed onto a 10 cm visual analogue scale (VAS) on the basis of a typical pooled SD of 2.5 cm in trials that assessed
pain using a VAS, and expressed as change based on an assumed standardised reduction of 0.72 standard deviation units in the control group.

[3] The median observed pain score at baseline across control groups in large osteoarthritis trials was 6.1 cm on a 10 cm VAS (Nuesch 2009).

[4] Downgraded (3 levels) because the effect was estimated from a meta-regression model using the standard error as independent variable and because included trials were generally of low quality and small sample size: only 2 out of 16 trials used adequate concealment of allocation, only 3 performed analyses according to the intention-to-treat principle, and the presence of large between trial heterogeneity.

[5] Standardised mean differences (SMDs) were back-transformed onto a 0 to 10 standardised WOMAC function score on the basis of a typical pooled SD of 2.1 in trials that
assessed function on WOMAC function scale and expressed as change based on an assumed standardised reduction of 0.58 standard deviation units in the control group.

[6] The median observed standardised WOMAC function score at baseline across control groups in large osteoarthritis trials was 5.6 units (Nuesch 2009).

[7] Downgraded (3 levels) because included trials were generally of low quality and small sample size: 1 out of 9 studies used adequate concealment of allocation methods, only 2 performed analyses according to the intention-to-treat principle, presence of moderate between trial heterogeneity, 9 out of 18 studies reported this outcome, likely leading to selective outcome reporting bias.

[8] Absolute response risks for function in the control groups were assumed 26% (see Methods section).

[9] Downgraded (2 levels) because the confidence interval crosses no difference in the pooled estimate, 1 out of 3 studies included all patients in this analysis, 3 out of 18 studies reported this outcome, likely leading to selective outcome reporting bias.

[10] Downgraded (1 level) because the confidence interval of the pooled estimate is wide and crossed no difference, 8 out of 18 studies reported this outcome, possibly leading to selective outcome reporting bias.

[11] Downgraded (2 levels) because 4 out of 18 studies reported this outcome, possibly leading to selective outcome reporting bias, the confidence interval of the pooled estimate is wide and crossed no difference.

BACKGROUND

Osteoarthritis is an age-related condition, occurring more frequently in women than in men. Its prevalence, causal associations and outcomes vary markedly according to the joint site affected (Jüni 2006). Osteoarthritis is characterised by focal areas of loss of articular cartilage in synovial joints, accompanied by subchondral bone changes, osteophyte formation at the joint margins, thickening of the joint capsule and mild synovitis (Solomon 1997). The objectives of management of knee osteoarthritis are to relieve pain and to maintain or improve function. Different modalities in physiotherapy have been suggested to improve the clinical course of knee osteoarthritis, with potentially fewer adverse effects than medical treatment (Bjordal 2007; Jamtvedt 2008), but some policy makers consider the evidence for effectiveness to be insufficient (Gezondheidsraad 1999).

Transcutaneous electrostimulation, the application of any electrical current through the skin with the aim of pain modulation, is a frequently used modality in knee osteoarthritis (Carroll 2001; Osiri 2000). It is based on the 'Gate-Control Theory' of pain perception as described by Melzack and Wall (Melzack 1965). The theory suggests that the stimulation of large diameter, (A-beta) primary sensory afferent cutaneous fibres activates inhibitory interneurons in the spinal cord dorsal horn and, thereby, may attenuate the transmission of nociceptive signals from small diameter A-delta and C fibres. Other suggested mechanisms include a stimulation of β endorphin production (Andersson 1976; Grimmer 1992; Mayer 1989) and even the potential for articular cartilage repair (Fary 2008; Haddad 2007).

Several types of electrostimulation are available. Conventional transcutaneous electrical nerve stimulation (TENS), in its narrow sense, uses moderate to high frequency current of 40 to 150 Hz and 50 to 100 µsec pulse width, typically at a low intensity, to stimulate sensory fibres. Several other types of TENS were subsequently developed, which differ in intensity, pulse width or frequency. Acupuncture-like TENS (AL TENS) uses a low frequency current of 0.5 to 10 Hz and a pulse width of > 150 µsec at a high intensity to stimulate both motor and sensory fibres. The stimulation may be painful, and the intensity of the current will depend on the patient's individual pain tolerance. Burst TENS was developed to minimise patients' discomfort, as experienced with AL TENS. It uses short bursts of high frequency current of typically 80 to 100 Hz, which are repetitively applied at low intensity and a burst frequency of around 5 Hz, to stimulate motor and sensory fibres. The intensity used is slightly higher than used with conventional TENS. Brief TENS uses a high frequency current of more than 100 Hz and 150 to 250 µsec pulse width at the maximal intensity tolerated by the patient to stimulate not only motor and sensory, but also nociceptor fibres. Modulation TENS combines several of the modalities above, typically using alternations of low and high frequency currents (Brosseau 2004; Sluka 2003). Classical interferential current stimulation simultaneously uses two non-modulated biphasic pulsed currents applied with two sets of electrodes with four electrical poles; one current is fixed at approximately 4000 Hz and the other ranging typically from 4000 to 4100 Hz. The superimposition of the two currents results in a new frequency with a range from 1 to 100 Hz (Wadsworth 1980). Modulated interferential current stimulation uses directed currents between two electrical poles and vectorially sums currents in the tissue, with a carrier frequency typically set at 4000 Hz, a beat frequency at 80 Hz, and a modulation frequency set between 0 to 150 Hz. The effective frequency is defined by the sum of beat and modulation frequency and varies between 80 and 230 Hz. The high frequency of the carrier currents in inferential current stimulation leads to a considerably lower impedance of skin and subcutaneous tissue as compared with conventional TENS and minimises patients' discomfort. Lastly, pulsed electrostimulation applies high frequency current of 100 Hz and a pulse width of 640 to 1800 µsec, typically using knee garments with flexible, embedded electrodes and a small battery-operated generator, allowing application times of several hours rather than 15 to 60 minutes, as is the case for any other of the modalities described above.

OBJECTIVES

We set out to compare transcutaneous electrostimulation with sham or no specific intervention in terms of effects on pain and function and safety outcomes in patients with knee osteoarthritis and to explore whether potential variation between trials could be explained by characteristics of the electrostimulation, by biases affecting individual trials or by publication bias.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials with a control group receiving a sham intervention or no intervention.

Types of participants

Studies including at least 75% of patients with clinically and/or radiologically confirmed osteoarthritis of the knee.

Types of interventions

Any type of transcutaneous electrostimulation with electrodes set to stimulate nerves supplying the knee joint area aiming at pain relief. We did not consider transcutaneous electrostimulation aiming at muscle strength enhancement, such as neuromuscular electrostimulation, and electrostimulation not directly aimed at stimulating nerves of the knee joint area, such as transcranial applications or transcutaneous spinal electroanalgesia. There were no restrictions related to the type of electrode used.

Types of outcome measures

Main outcomes

Main outcomes were pain intensity as the effectiveness outcome (Altman 1996; Pham 2004) and withdrawals or drop-outs because of adverse events as the safety outcome. If data on more than one pain scale were provided for a trial, we referred to a previously described hierarchy of pain-related outcomes (Jüni 2006; Reichenbach 2007) and extracted data on the pain scale that is highest on this hierarchy:

1. Global pain
2. Pain on walking
3. WOMAC osteoarthritis index pain subscore
4. Composite pain scores other than WOMAC
5. Pain on activities other than walking
6. Rest pain or pain during the night
7. WOMAC global algofunctional score
8. Lequesne osteoarthritis index global score
9. Other algofunctional scale
10. Patient's global assessment
11. Physician's global assessment

If pain outcomes were reported at several time points, we extracted the estimate at the end of the treatment period.

Secondary outcomes

Secondary outcomes were function, the number of patients experiencing any adverse event and patients experiencing any serious adverse events. We defined serious adverse events as events resulting in hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality/birth defect of offspring, life-threatening events or death.

If data on more than one function scale were provided for a trial, we extracted data according to the hierarchy presented below.

1. Global disability score
2. Walking disability
3. WOMAC disability subscore
4. Composite disability scores other than WOMAC
5. Disability other than walking
6. WOMAC global scale
7. Lequesne osteoarthritis index global score
8. Other algofunctional scale
9. Patient's global assessment
10. Physician's global assessment

If function outcomes were reported at several time points, we extracted the estimate at the end of the treatment period. For safety outcomes, we extracted end of trial data.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 3), MEDLINE and EMBASE through the Ovid platform (www.ovid.com), CINAHL through EBSCOhost, Physiotherapy Evidence Database (PEDro, http:/ / www.pedro.fhs.usyd.edu.au/, from 1929 onwards), all from implementation to 5 August 2008, using a combination of keywords and text words related to electrostimulation combined with keywords and text words related to osteoarthritis and a validated filter for controlled clinical trials (Dickersin 1994). The search strategy is presented in Appendix 1 and Appendix 2.

Searching other sources

We manually searched conference proceedings, used Science Citation Index to retrieve reports citing relevant articles, contacted content experts and trialists and screened reference lists of all obtained articles, including related reviews. Finally, we searched several clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com, www.actr.org.au, www.umin.ac.jp/ ctr) to identify ongoing trials.

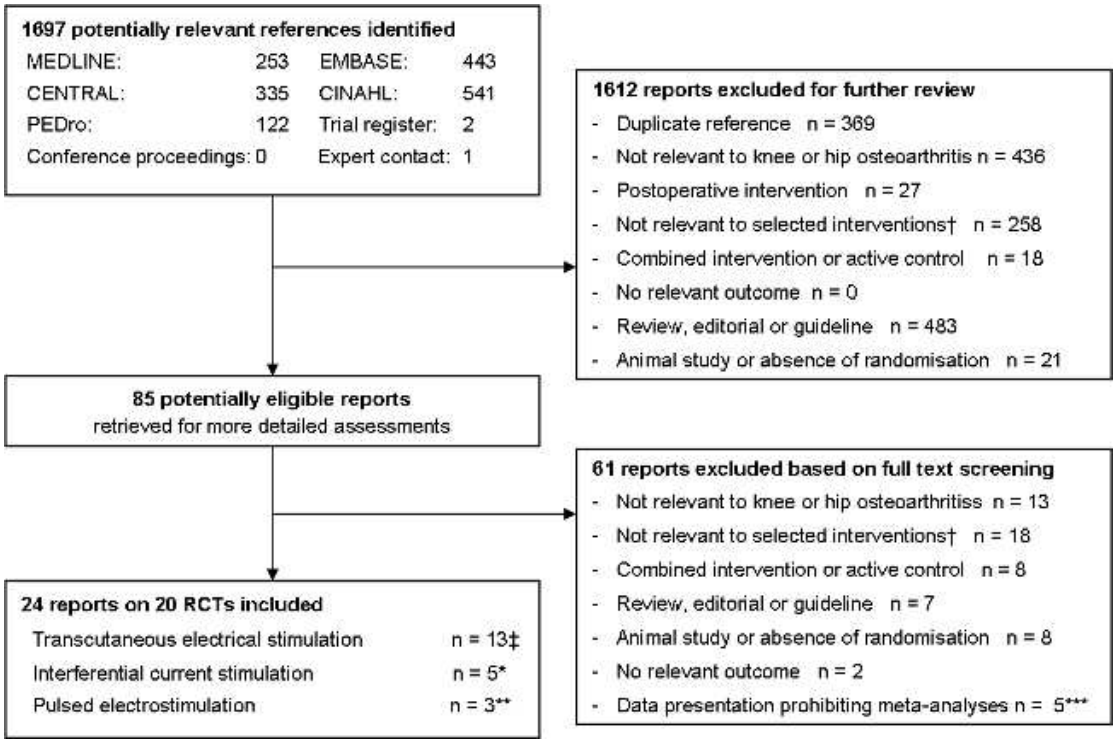
The last update of the manual search was on 2 February 2009.

Data collection and analysis

Selection of studies

Two review authors evaluated independently all titles and abstracts for eligibility (see Figure 1). We resolved disagreements by discussion. We applied no language restrictions. If multiple reports described the same trial, we considered all.

Figure 1. Flow chart



Data collection

Two review authors (AR and EN, RS or LK) extracted trial information independently using a standardised, piloted data extraction form accompanied by a codebook. We resolved disagreements by consensus or discussion with a third author (SR or PJ). We extracted the type of electrostimulation, including the mode of function (types of stimulator and electrode), the pulse form (intensity, rate and width), the electrode placement site and the frequency and duration of treatment. Other data extracted included the type of control intervention used, patient characteristics (gender, average age, duration of symptoms, type of joint), characteristics of pain, function and safety outcomes, design, trial size, trial duration (defined as time from randomisation until end of follow up), type and source of financial support and publication status. When necessary, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data from the first period only. Whenever possible, we used results from an intention-to-treat analysis. If effect sizes could not be calculated, we contacted the authors for additional data.

Quality assessment

Two review authors (AR and EN, RS or LK) independently assessed randomisation, blinding, selective outcome reporting and handling of incomplete outcome data in the analyses (Higgins 2008; Jüni 2001). We resolved disagreements by consensus or discussion with a third author (SR or PJ). We assessed two components of randomisation: generation of allocation sequences and concealment of allocation. We considered generation of sequences adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate included random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling of cards and drawing of lots. Trials using an unpredictable allocation sequence were considered randomised; trials using potentially predictable allocation mechanisms, such as alternation or the allocation of patients according to date of birth, were considered quasi-randomised. We considered allocation concealment adequate if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next; methods considered adequate included central randomisation and sequentially numbered, sealed, opaque envelopes. We considered blinding of patients adequate if a sham intervention was used that was identical in appearance from the control intervention. Transcutaneous electrostimulation generally does not allow blinding of therapists, whereas pain as the main effectiveness outcome is patient-reported by definition. Therefore, we did not assess blinding of therapists and outcome assessors. We considered handling of incomplete outcome data adequate if all randomised patients were included in the analysis (intention-to-treat principle). Finally, we used GRADE to describe the quality of the overall body of evidence (Higgins 2008; Guyatt 2008), defined as the extent of confidence in the estimated treatment benefits and harms.

Data synthesis

We summarised continuous outcomes using standardised mean differences (SMD), with the differences in mean values at the end of treatment across treatment groups divided by the pooled standard deviation. If differences in mean values at the end of the treatment were unavailable, we used differences in mean changes. If some of the required data were unavailable, we used approximations as previously described (Reichenbach 2007). A SMD of -0.20 standard deviation units can be considered a small difference between experimental and control group, a SMD of -0.50 a moderate difference, and -0.80 a large difference (Cohen 1988; Jüni 2006). SMDs can also be interpreted in terms of the percent of overlap of the experimental group's scores with the scores of the control group. A SMD of -0.20 indicates an overlap in the distributions of pain or function scores in about 85% of cases, a SMD of -0.50 in approximately 67% and a SMD of -0.80 in about 50% of cases (Cohen 1988; Jüni 2006). On the basis of a median pooled SD of 2.5 cm found in large-scale osteoarthritis trials that assessed pain using a 10 cm visual analogue scale (VAS) (Nuesch 2009), SMDs of -0.20, -0.50 and -0.80 correspond to approximate differences in pain scores between experimental and control groups of 0.5, 1.25 and 2.0 cm on a 10 cm VAS. SMDs for function were back transformed to a standardised WOMAC disability score (Bellamy 1995) ranging from 0 to 10 on the basis of a median pooled SD of 2.1 units observed in large-scale osteoarthritis (Nuesch 2009). We expressed binary outcomes as relative risks.

We used standard inverse-variance random-effects meta-analysis (DerSimonian 1986) to combine trials overall and stratified according to gross categories of electrostimulation (TENS, interferential current stimulation or pulsed electrostimulation). We quantified heterogeneity between trials using the I^2 statistic (Higgins 2003), which describes the percentage of variation across trials that is attributable to heterogeneity rather than to chance and the corresponding χ^2 test. I^2 values of 25%, 50% and 75% may be interpreted as low, moderate and high between-trial heterogeneity, although the interpretation of I^2 depends on the size and number of trials included (Rucker 2008). The association between trial size and treatment effects was investigated in funnel plots, plotting effect sizes on the vertical axis against their standard errors on the horizontal axis. We assessed asymmetry by the asymmetry coefficient: the difference in effect size per unit increase in standard error (Sterne 2001), which is mainly a surrogate for sample size, and used uni-variable meta-regression analysis to predict treatment effects in trials as large as the largest trials included in the meta-analysis, using the standard error as the explanatory variable (Shang 2005). In view of the biased nature of the predominantly small trials included in the meta-analysis of pain intensity, we considered the predicted estimates of effectiveness more reliable than the pooled estimates. For the analysis on the effectiveness outcomes pain and function, we differentiated between TENS, interferential current stimulation and pulsed electrostimulation. Then, we performed effectiveness analyses stratified by

the following trial characteristics: concealment of allocation, use of a sham intervention in the control group, blinding of patients, analysis in accordance with the intention-to-treat principle, trial size, difference in the use of analgesic cointerventions, specific type of electrostimulation, duration of stimulation per session, number of sessions per week, duration of electrostimulation per week as an overall measure of treatment intensity, and duration of treatment period. A cut-off of 200 patients was used to distinguish between small and large trials; a sample size of 100 patients per group will yield more than 80% power to detect a small to moderate SMD of -0.40 at a two-sided P of 0.05. For the analysis according to specific type of stimulation, we distinguished between high frequency TENS, burst TENS, modulation TENS, low frequency TENS, interferential current stimulation or pulsed electrostimulation. We classified conventional TENS and brief TENS as high frequency TENS. Cut-offs of 20 and 60 minutes were used for the duration of electrostimulation per session, corresponding to the typical treatment duration in physical therapy, and the optimum stimulation duration suggested by Cheing 2003. A cut-off of four weeks was used for the overall duration of the treatment period (time from randomisation to last session), in line with the previous version on this review. Cut-offs of three and seven were used for the number of sessions per week; one and five hours for the duration of electrostimulation per week, corresponding to the distribution of tertiles. We used uni-variable random-effects meta-regression models to determine whether treatment effects were affected by these factors (Thompson 1999). Then, we converted SMDs of pain intensity and function to odds ratios (Chinn 2000) to derive numbers needed to treat (NNT) to cause one additional treatment response on pain or function as compared with control, and numbers needed to harm (NNH) to cause one additional adverse outcome. We defined treatment response as a 50% improvement in scores (Clegg 2006), which corresponds to an average decrease of 1.2 standard deviation units. Based on the median standardised pain intensity at baseline of 2.4 standard deviation units and the median standardised decrease in pain scores of 0.72 standard deviation units observed in large osteoarthritis trials (Nuesch 2009), we calculated that a median of 31% of patients in the control group would achieve an improvement of pain scores of 50% or more. This percentage was used as the control group response rate to calculate NNTs for treatment response on pain. Based on the median standardised WOMAC function score at baseline of 2.7 standard deviation units and the median standardised decrease in function scores of 0.58 standard deviation units (Nuesch 2009), 26% of patients in the control group would achieve a reduction in function of 50% or more. Again, this percentage was used as the control group response rate to calculate NNTs for treatment response on function. We used median risks of 150 patients with adverse events per 1000 patient-years, four patients with serious adverse events per 1000 patient-years and 17 drop-outs due to adverse events per 1000 patient-years observed in placebo groups in large osteoarthritis trials (Nuesch 2009) to calculate NNHs for safety outcomes. We performed analyses in RevMan version 5 (RevMan 2008) and STATA version 10.1 (StataCorp, College Station, Texas). All P values are two-sided.

RESULTS

Description of studies

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

We identified 1697 references to articles and considered 85 to be potentially eligible (Figure 1). Twenty-two reports describing 18 completed trials in 813 patients and two protocols describing uncompleted trials (Fary 2008; Palmer 2007) met our inclusion criteria. Six trials evaluated high frequency TENS (Bal 2007; Cetin 2008; Cheing 2002; Cheing 2003; Law 2004a; Smith 1983), one high frequency and burst TENS (Grimmer 1992), one high frequency TENS and interferential current stimulation (Adedoyin 2005), one low frequency, high frequency and modulation TENS with alternating low and high frequency current (Law 2004), one burst TENS (Fargas-Babjak 1989), two low frequency TENS (Ng 2003; Yurtkuran 1999), four interferential current stimulation (Adedoyin 2002; Defrin 2005; Itoh 2008; Quirk 1985), and three evaluated pulsed electrostimulation (Fary 2008; Garland 2007; Zizic 1995). The protocol of Palmer 2007 did not specify which type of TENS would be used.

The description of the uncompleted trials can be found in the ' Characteristics of ongoing studies' table. Of the completed trials, 17 trials used a parallel group and one a 2 x 2 factorial design (Itoh 2008). Twelve trials used a sham intervention in the control group, five used no intervention (Adedoyin 2005; Cetin 2008; Itoh 2008; Quirk 1985; Ng 2003) and one trial had both a sham and a no intervention control (Cheing 2002). Standardised cointerventions, provided in both experimental and control groups, were used in five trials with no intervention controls (Adedoyin 2005; Cetin 2008; Cheing 2002; Ng 2003; Quirk 1985) and in two trials with a sham intervention (Adedoyin 2002; Bal 2007). Cetin 2008 used hot packs and exercise, Adedoyin 2002 dietary advice and exercise, Quirk 1985, Cheing 2002 and Adedoyin 2005 exercise, Bal 2007 used infra-red therapy and Ng 2003 an educational pamphlet. In addition, Itoh 2008 assigned 50% of patients to acupuncture using a factorial design.

Characteristics of the currents varied considerably, even within a specific type of electrostimulation. In the three trials evaluating low frequency TENS, pulse width and pulse frequency ranged from 200 μsec and 2 Hz to 1000 μsec and 4 Hz, with intensities set to reach a comfortable level in one (Law 2004), and resulting in muscle contraction in two trials (Ng 2003; Yurtkuran 1999). In trials of high frequency TENS, pulse width and pulse frequency ranged from 80 μsec and 32 Hz (Smith 1983) to 200 μsec and 100 Hz (Cheing 2003), with the majority of intensities described

as strong but comfortable. In trials of burst TENS, Fargas-Babjak 1989 used a pulse frequency of 200 Hz, a train length of 125 μsec and a repetition frequency of 4 Hz with intensity increased up to the patients' limits of tolerability, while Grimmer 1992 used a pulse frequency of 80 Hz, an unclear train length and pulse width and a repetition frequency of 3 Hz, with the intensity resulting in a strong, tolerable tingling sensation and visible, but comfortable muscle contraction. In the five trials of interferential current stimulation, the beat frequency ranged from 30 to 130 Hz and intensities resulted typically in tingling sensations in four trials (Adedoyin 2002; Adedoyin 2005; Itoh 2008; Quirk 1985), and pain in one (Defrin 2005). The two trials of pulsed electrostimulation were the only ones to use intensities below the sensory threshold (Garland 2007; Zizic 1995). The trials used the same device, which produces monophasic, spike-shaped pulses in a frequency of 100 Hz. The intensity of the current was initially increased until a tingling sensation was felt and subsequently reduced until this sensation disappeared.

The trials differed in type, number and localisation of electrodes used (see 'Characteristics of included studies'). The median duration of electrostimulation per session was 25 minutes (range 15 minutes to 8.2 hours), with a duration of 15 to 20 minutes in 10 trials (Adedoyin 2005; Adedoyin 2002; Cetin 2008; Cheing 2003; Defrin 2005; Itoh 2008; Quirk 1985; Ng 2003; Smith 1983; Yurtkuran 1999), 30 to 40 minutes in six (Bal 2007; Cheing 2003; Fargas-Babjak 1989; Grimmer 1992; Law 2004a; Law 2004) and 60 minutes or more in 4 trials (Cheing 2002; Cheing 2003; Garland 2007; Zizic 1995). The median number of treatment sessions per week was 3.5 (range 1 to 14), with up to three sessions per week in eight trials (Adedoyin 2002; Adedoyin 2005; Cetin 2008; Defrin 2005; Grimmer 1992; Itoh 2008; Quirk 1985; Smith 1983), four to six in seven (Bal 2007; Cheing 2002; Cheing 2003; Law 2004; Law 2004a; Ng 2003; Yurtkuran 1999) and seven or more in three trials (Fargas-Babjak 1989; Garland 2007; Zizic 1995). This resulted in a median duration of electrostimulation of 1.5 hours per week (range 15 minutes to 57.4 hours). The median length of the treatment period was four weeks (range one day to 12 weeks).

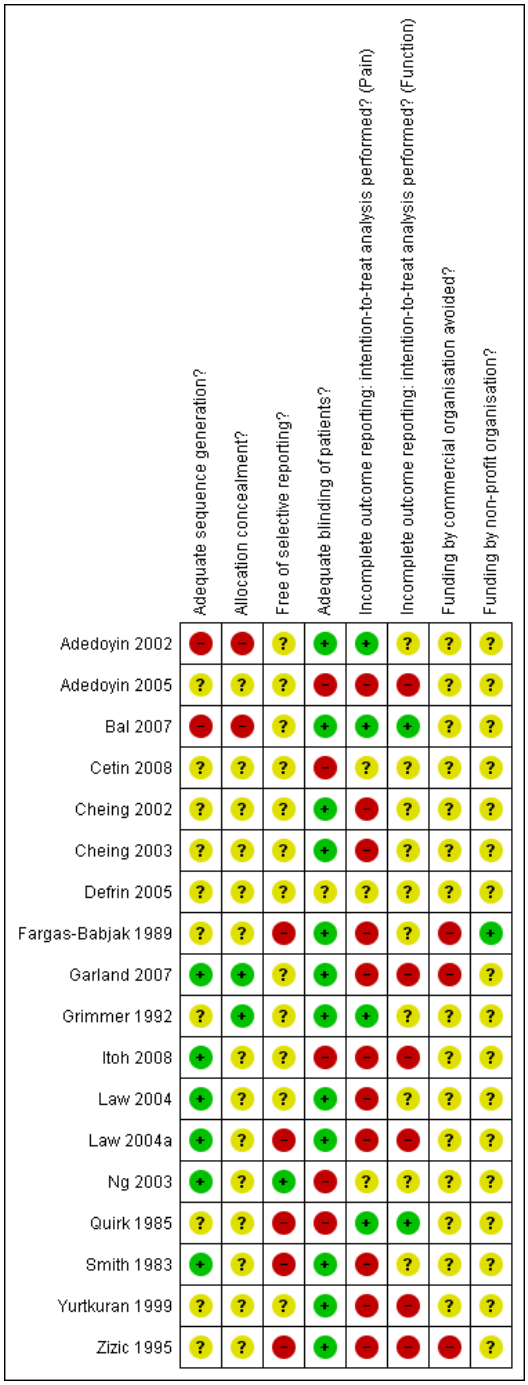
All but one trial explicitly included patients with knee osteoarthritis only, with the diagnosis based on clinical and/or radiographic evidence. Fargas-Babjak 1989 included patients with either knee or hip osteoarthritis, and failed to report the percentage of patients with knee osteoarthritis, but it was considered likely that this percentage was above 75%. The majority of patients had a clinical severity requiring simple non-surgical treatments (Jüni 2006). In one trial of pulsed electrostimulation, the majority of patients (41 out of 58) were candidates for total knee arthroplasty, however (Garland 2007). The description of patient characteristics was generally poor. Only four trials (Bal 2007; Garland 2007; Law 2004a; Yurtkuran 1999) reported the average disease duration, which ranged from two to 8.4 years.

Four cross-over trials could not be included because of incomplete reporting, which did not allow the distinction between treatment phases (Lewis 1984; Lewis 1985; Lewis 1994; Taylor 1981). All but Lewis 1985 were included in the previous version of this review (Osiri 2000). Three other trials were excluded because of an active control intervention using another type of electrostimulation (Burch 2008; Jensen 1991; Volklein 1990). Detailed reasons for exclusion are displayed in 'Characteristics of excluded studies'.

Risk of bias in included studies

Figure 2 summarises the methodological characteristics and source of funding of included trials. One trial reported both adequate sequence generation and adequate concealment of allocation (Garland 2007), five trials reported only adequate sequence generation (Itoh 2008; Law 2004; Law 2004a; Ng 2003; Smith 1983) and one trial reported adequate concealment, but provided insufficient detail on the generation of allocation sequence (Grimmer 1992). Two trials were quasi-randomised, one used alternation to allocate patients to experimental and control intervention (Adedoyin 2002), the other allocated patients according to hospital registration number (Bal 2007). In the remaining nine trials, low quality of reporting hampered any judgement regarding sequence generation and concealment of allocation.

Figure 2. Methodological characteristics and source of funding of included trials. (+) indicates low risk of bias, (?) unclear and (-) a high risk of bias on a specific item.



Six trials (Fargas-Babjak 1989; Garland 2007; Grimmer 1992; Law 2004; Law 2004a; Zizic 1995) were described as double-blind. Thirteen trials used sham interventions, all using identical devices in experimental and control groups (Adedoyin 2002; Bal 2007; Cheing 2002; Cheing 2003; Defrin 2005; Fargas-Babjak 1989; Garland 2007; Grimmer 1992; Law 2004a; Law 2004; Smith 1983; Yurtkuran 1999; Zizic 1995). In 10 out of 13 trials, sham devices had broken leads so that no current could pass, whereas the indicator light or digital display of intensity control functioned normally. In the two pulsed electrostimulation trials, all patients were instructed to increase the intensity until a tingling sensation was felt, after which they were asked to reduce intensity just below the perception (sensory) level. Pulsed electrostimulation sham devices were adapted with an automatic shut-off as soon as the amplitude was reduced (Garland 2007; Zizic 1995). Only the sham device used in Defrin 2005 was not considered to lead to adequate patient blinding, as the sham device was described as shut off. Only the two trials of pulsed electrostimulation, however, which used currents below the sensory threshold, were deemed to have fully credible blinding of patients (Garland 2007; Zizic 1995).

Sixteen out of 18 completed trials contributed to the analysis of pain outcomes. Of these, only three trials (Adedoyin 2002; Bal 2007; Grimmer 1992), which had analysed all randomly assigned patients, were considered to have an intention-to-treat analysis of pain outcomes at end of treatment. In three trials (Cetin 2008; Defrin 2005; Ng 2003) it was unclear whether exclusions of randomised patients from the analysis had occurred, in five trials (Fargas-Babjak 1989; Garland 2007; Law 2004; Law 2004a; Yurtkuran 1999) exclusions were reported, but their percentage remained unclear and in the remaining six trials the median reported exclusion rate was 7% in the experimental and 11.5% in the control groups (range 0% to 25% in both experimental and control groups). Two out of nine trials contributing to the analysis of function outcomes were considered to have an intention-to-treat analysis (Bal 2007; Quirk 1985). In one trial (Cetin 2008) it was unclear whether exclusions of randomised patients from the analysis had occurred, in three trials (Garland 2007; Law 2004a; Yurtkuran 1999) exclusions were reported, but their percentage remained unclear and in the remaining three trials the median reported exclusion rate was 11.5% in experimental and 12% in control groups (range 0% to 25% in experimental, and 11% to 25% in control groups, respectively).

Only three trials explicitly specified primary outcomes (Adedoyin 2002; Itoh 2008; Zizic 1995), although one of these specified more than two (Zizic 1995). Only one trial reported a sample size calculation (Adedoyin 2005). None of the trials had a sufficient sample size of at least 200 patients overall to achieve sufficient power for detecting a small to moderate SMD. Only three trials reported their source of funding: one was supported by a non-profit organisation and a commercial body (Fargas-Babjak 1989), the other two by a commercial body only (Garland 2007; Zizic 1995).

For the effectiveness outcomes pain and function, the quality of the evidence (Guyatt 2008) was classified as very low in view of the risk of bias in the included, predominantly small trials of questionable quality, the large heterogeneity between trials, the potential for selective reporting of function outcomes and the exploratory nature of the model used to predict SMDs of pain in trials as large as the largest trials ('Summary of findings for the main comparison'). For the safety outcomes, the quality of the evidence (Guyatt 2008) was classified as moderate to low, again because of the predominantly small trials of questionable quality, the small number of trials reporting the outcomes and the small number of events resulting in imprecise estimates.

Effects of interventions

See: **Summary of findings for the main comparison**

Knee pain

Sixteen trials with 18 comparisons (726 patients) contributed to the meta-analysis of pain outcomes (Figure 3). The analysis suggested an overall large SMD of -0.86 (95% CI -1.23 to -0.49), which corresponds to a difference in pain scores of 2.1 cm on a 10 cm VAS between electrostimulation and control, favouring electrostimulation. Within the types of electrostimulation, a very large effect was found for interferential current stimulation (SMD -1.20, 95% CI -1.99 to -0.42), a large effect in TENS (SMD -0.85, 95% CI -1.36 to -0.34) and a moderate effect in pulsed electrostimulation (SMD -0.41, 95% CI -0.77 to -0.05). However, interaction tests provided little evidence for differences between different types. Pooling all types of electrostimulation, an I^2 of 80% indicated a high degree of between-trial heterogeneity (P for heterogeneity < 0.001), which was not substantially reduced when pooling types of electrostimulation separately. Four trials (Cheing 2003; Defrin 2005; Law 2004; Law 2004a) showed unrealistically large SMDs of twice to three times the magnitude of what would be expected for total joint replacement (Jüni 2006). The funnel plot appeared asymmetrical (Figure 4, P for asymmetry < 0.001) and the corresponding asymmetry coefficient was -7.6 (95% CI -10.6 to -4.5). This coefficient indicates that the beneï¬t of electrostimulation increases by 7.6 standard deviation units for each unit increase in the standard error of the SMD, which is mainly a surrogate for sample size. The predicted SMD in trials as large as the largest trial (Zizic 1995, n = 71, standard error = 0.24) was -0.07 (95% CI -0.46 to 0.32), which corresponds to a difference in pain scores of 0.2 cm on a 10 cm VAS between electrostimulation and control. Referring to a median pain intensity of 6.1 cm in placebo groups at baseline, this corresponds to a difference of 4% improvement (95% CI -13% to +20%) between electrostimulation and control ('Summary of findings for the main comparison').

Figure 3. Forest plot of 16 trials comparing the effects of any type of transcutaneous electrostimulation and control (sham or no intervention) on knee pain. Values on x-axis denote standardised mean differences. The plot is stratified according to type of electrostimulation. Law 2004 reported on knee level, we inflated the standard error with sqrt(number knees)/sqrt(number patients) to correct for clustering of knees within patients. Adedoyin 2005 and Cheing 2002 contributed with two comparisons each. In Adedoyin 2005, the standard error was inflated and the number of patients in the control group was halved to avoid duplicate counting of patients when including 2 both comparisons in the overall meta-analysis. Data relating to the 3, 2, 3 and 4 active intervention arms in Cheing 2003, Grimmer 1992, Law 2004 and Defrin 2005, respectively, were pooled.

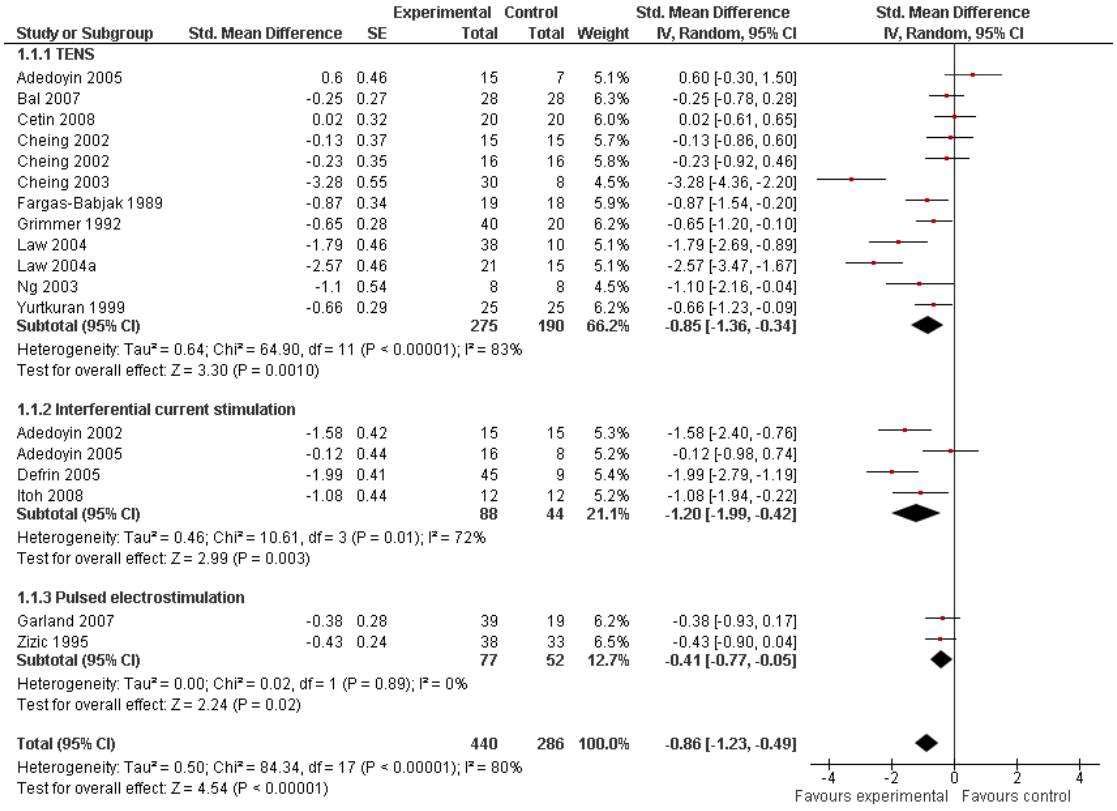


Figure 4. Funnel plot for effects on knee pain.
Numbers on x-axis refer to standardised mean differences (SMDs), on y-axis to standard errors of SMDs.

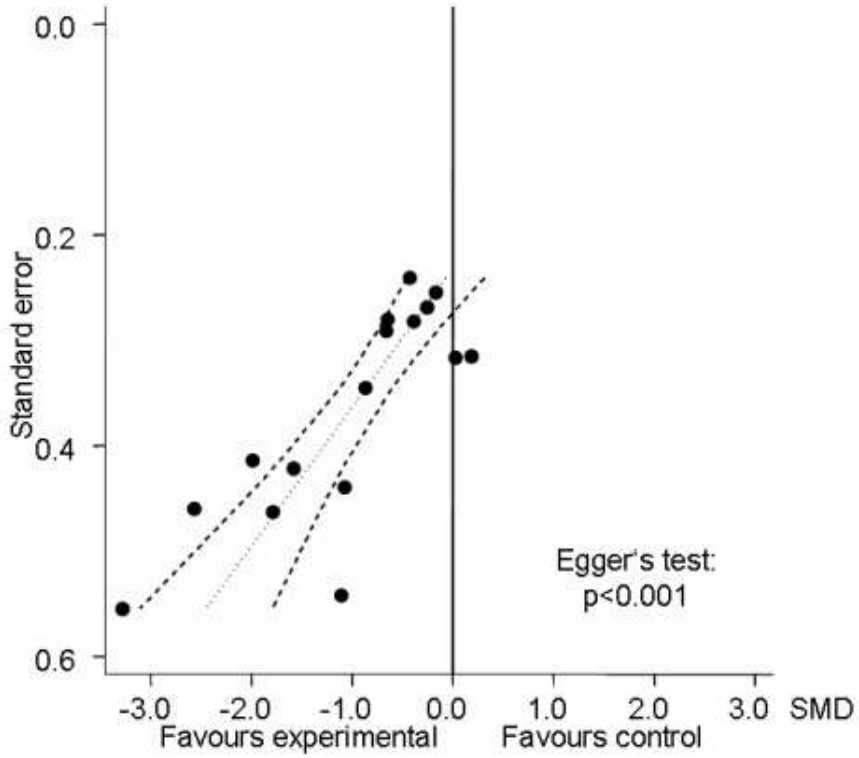


Table 1 presents results from stratified analyses. Estimates of SMD varied to some degree depending on concealment of allocation, adequacy of patient blinding, use of analgesic cointerventions and characteristics of electrostimulation, but 95% CIs of SMDs were wide and tests of interaction and tests for trend not statistically significant. There was little evidence to suggest that SMDs depended on the type of electrostimulation used (P for interaction = 0.94). Contrary to what would be expected in the presence of relevant placebo effects, we found some evidence towards larger benefits of electrostimulation in trials with a sham intervention as compared with trials without (P for interaction = 0.12). In addition, there was some evidence for larger benefits of electrostimulation associated with short durations of the overall treatment period of less than four weeks as compared with four weeks or more (P for interaction = 0.14). The analysis could not be stratified according to sample size, because none of included trials reached the prespecified sample size of 200 patients to be considered as adequately sized.

Table 1. Results of stratified analyses of pain outcomes

Variable	N of trials	N of patients (experimental)	N of patients (control)	Pain intensity	Heterogeneity	P for interaction
	n	n	n	SMD (95% CI)	I^2 (%)	
All trials	16	440	286	-0.86 (-1.23 to -0.49)	80%	
Allocation concealment						0.47
Adequate	2	79	39	-0.52 (-0.91 to -0.13)	0%	
Inadequate or unclear	14	361	247	-1.03 (-1.49 to -0.57)	84%	
Type of control intervention*						0.12
Sham intervention	12	354	216	-1.13 (-1.59 to -0.67)	82%	
No control intervention	5	86	70	-0.31 (-0.80 to 0.19)	58%	
Blinding of patients						0.37
Adequate	11	309	205	-1.05 (-1.52 to -0.59)	82%	
Inadequate or unclear	6	131	79	-0.63 (-1.31 to 0.05)	81%	
Use of analgesic cointerventions						0.36
Similar between groups	4	124	83	-0.57 (-1.16 to 0.02)	74%	
Not similar or unclear	12	316	23	-1.10 (-1.60 to -0.59)	84%	

Table 1. Results of stratified analyses of pain outcomes (*Continued*)

Intention-to-treat analysis						0.73
Yes	3	83	63	-0.76 (-1.43 to -0.09)	72%	
No or unclear	13	357	223	-1.00 (-1.48 to -0.53)	84%	
Type of ES**						0.94
High frequency TENS	8	177	139	-0.82 (-1.51 to -0.12)	86%	
Burst TENS	2	39	38	-0.85 (-1.32 to -0.38)	0%	
Modulation TENS	1	13	3	-1.41 (-2.92 to 0.10)	N/A	
Low frequency TENS	3	46	40	-0.82 (-1.29 to -0.34)	0%	
Interferential current stimulation	4	88	44	-1.20 (-1.99 to -0.42)	71%	
Pulsed ES	2	77	52	-0.41 (-0.77 to -0.05)	0%	
Duration of ES per session†						0.69‡
≤ 20 minutes	8	166	112	-0.95 (-1.55 to -0.35)	78%	
30 to 40 minutes	6	156	99	-1.45 (-2.28 to -0.62)	85%	
≥ 60 minutes	4	118	91	-0.47 (-0.96 to 0.02)	58%	
Number of sessions per week						0.90‡

Table 1. Results of stratified analyses of pain outcomes (*Continued*)

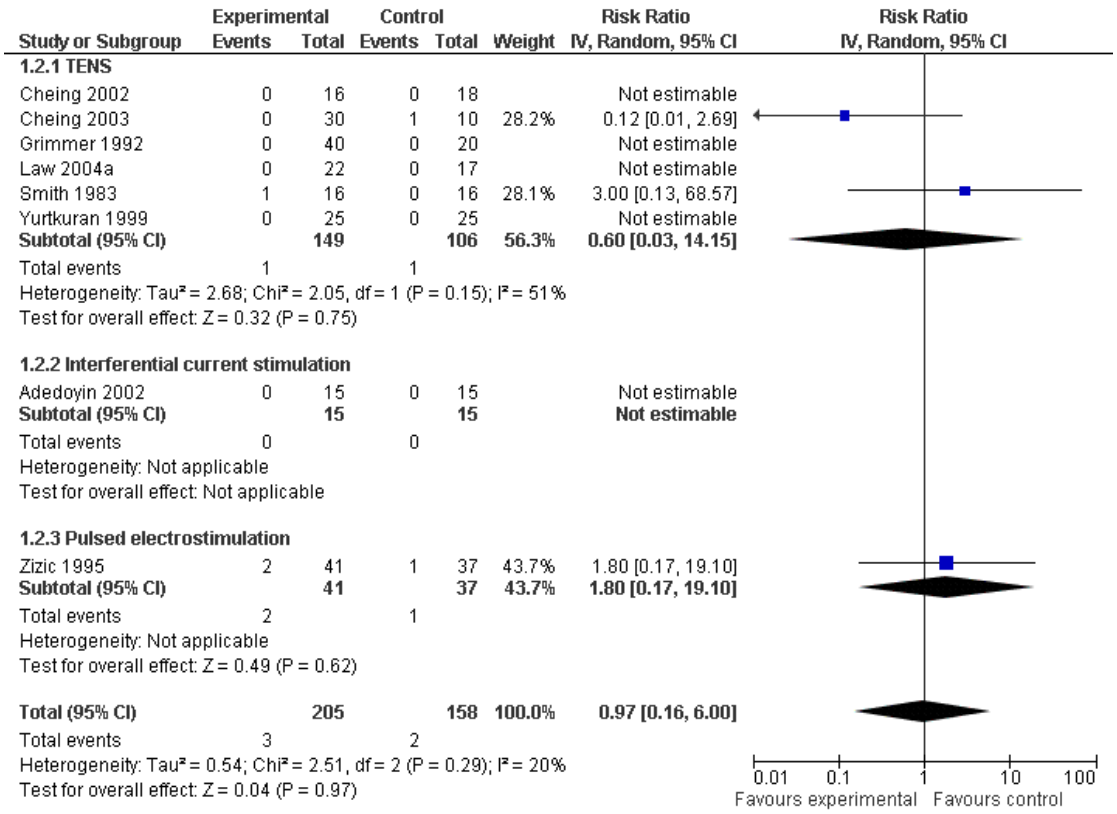
≤ 3	6	163	91	-0.81 (-1.48 to -0.14)	82%	
4 to 6	7	182	125	-1.33 (-2.11 to -0.54)	88%	
≥ 7	3	96	70	-0.51 (-0.83 to -0.19)	0%	
Duration of ES per week* **						0.74‡
≤1 hour	5	123	71	-0.85 (-1.72 to 0.01)	86%	
> 1 to 5 hours	8	180	122	-1.42 (-2.11 to -0.74)	81%	
> 5 hours	5	137	109	-0.53 (-0.96 to -0.11)	55%	
Duration of treatment period						0.14
< 4 weeks	7	190	114	-1.39 (-2.13 to -0.66)	86%	
≥ 4 weeks	9	250	172	-0.64 (-1.06 to -0.22)	75%	

ES: electrostimulation; *In Cheing 2002, two independent comparisons contributed in the two different strata. **Adedoyin 2005, Grimmer 1992 and Law 2004 contributed to two, two and three different strata: high-frequency TENS and interferential current stimulation, high-frequency TENS and burst, and high-, low-frequency and modulation TENS, respectively. † = Cheing 2003 contributed to all three different strata, with the same 8 control patients displayed in each stratum. ‡ = P values from test for trend.

Withdrawals or drop-outs because of adverse events

Eight trials (348 patients) contributed to the meta-analysis of patients withdrawn or dropped out because of adverse events (Figure 5). Of these, four TENS trials and one interferential current stimulation trial reported that no withdrawals or drop-outs due to adverse events had occurred, neither in experimental nor in control groups, therefore relative risks could not be estimated. In the remaining three trials, there was no evidence that transcutaneous electrostimulation is unsafe (relative risk 0.97), but 95% confidence intervals were wide and ranged from 0.16 to 6.00. Pooling all types of electrostimulation, an I^2 of 20% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.29).

Figure 5. Forest plot of 8 trials comparing patients withdrawn or dropped out because of adverse events between any transcutaneous electrostimulation and control (sham or no intervention). Values on x-axis denote risk ratios. Risk ratios could not be estimated in 5 trials, because no drop-out occurred in either group. The plot is stratified according to type of electrostimulation. Data relating to the 3 and 2 active intervention arms in Cheing 2003 and Grimmer 1992, respectively, were pooled.



Function

Nine trials (407 patients) contributed to the meta-analysis of function. The analysis suggested a small SMD of -0.34 (95% CI -0.54 to -0.14, Figure 6), which corresponds to a difference in function scores of 0.7 units on a standardised WOMAC disability scale ranging from 0 to 10, favouring electrostimulation. Referring to a median function score of 5.6 units in placebo groups at baseline, this corresponds to a difference of 20% improvement

(95% CI +11% to +29%) between electrostimulation and control ('Summary of findings for the main comparison'). The estimated difference in the percentage of treatment responders between patients allocated to electrostimulation and patients allocated to placebo of 3% translated into an NNT to cause one additional treatment response on function of 29 (95% CI 19 to 69) ('Summary of findings for the main comparison'). Differences between types of electrostimulation were not statistically significant. An I^2 of 0% suggested no between-trial heterogeneity (P for heterogeneity = 0.57). The funnel plot did not appear asymmetrical (Figure 7, P for asymmetry = 0.52). The corresponding asymmetry coefficient was 1.4 (95% CI, -3.5 to 6.3).

Figure 6. Forest plot of 9 trials comparing the effects of any type of transcutaneous electrostimulation and control (sham or no intervention) on function. Values on x-axis denote standardised mean differences. The plot is stratified according to type of electrostimulation. In Adedoyin 2005, the standard error was inflated and the number of patients in the control group was halved to avoid duplicate counting of patients when including both comparisons in the overall meta-analysis.

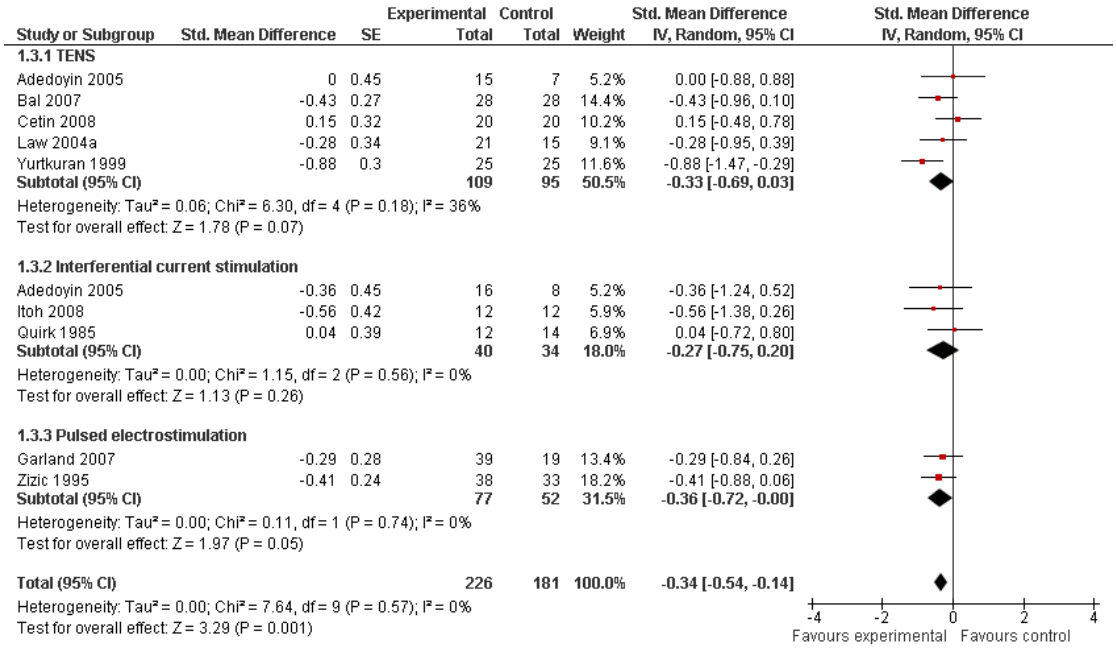


Figure 7. Funnel plot for effects on functioning of the knee.
Numbers on x-axis refer to standardised mean differences (SMDs), on y-axis to standard errors of SMDs.

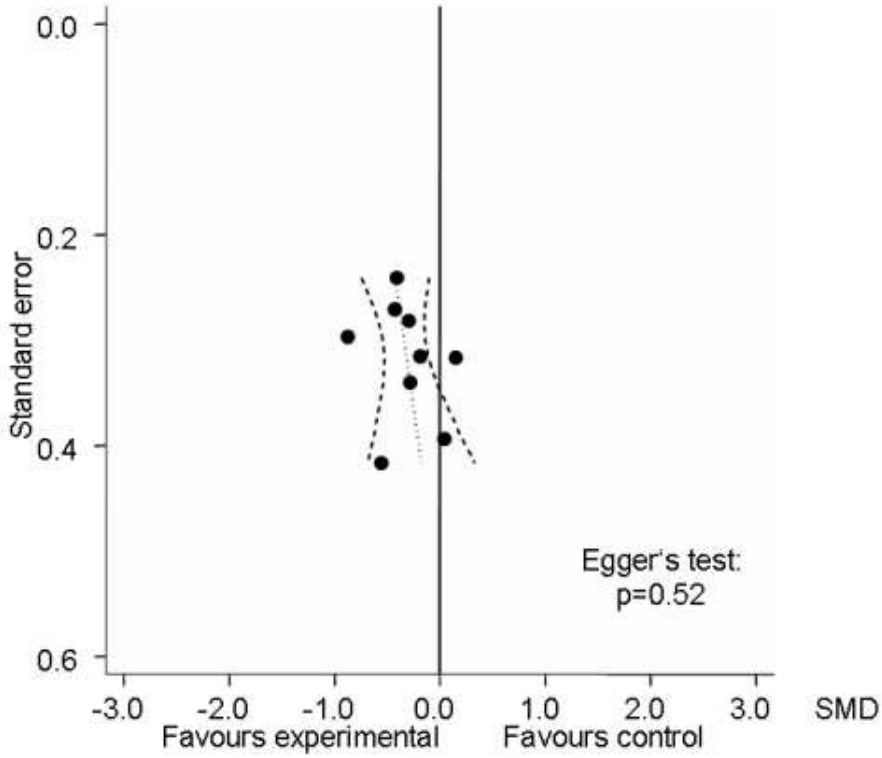


Table 2 presents results from stratified analyses. Estimates of SMD varied to some degree depending on type of control intervention, adequacy of patient blinding, characteristics of electrostimulation and overall treatment period, but 95% CIs of SMDs were wide and tests for interaction and tests for trend not statistically significant. There was little evidence to suggest that SMDs depended on the type of electrostimulation used (P for interaction = 0.32). Again, the analysis could not be stratified according to sample size, because none of included trials reached the pre-specified sample size of 200 patients to be considered as adequately sized.

Table 2. Results of stratified analyses of function

Variable	N of trials	N of patients (experimental)	N of patients (control)	Function	Heterogeneity	P for interaction
				SMD (95% CI)	I^2 (%)	
All trials	9	226	181	-0.34 (-0.54 to -0.14)	0%	
Allocation concealment						0.88
Adequate	1	39	19	-0.29 (-0.85 to 0.26)	N/A	
Inadequate or unclear	8	187	162	-0.34 (-0.56 to -0.12)	5%	
Type of control intervention						0.14
Sham intervention	5	151	120	-0.46 (-0.70 to -0.21)	0%	
No control intervention	4	75	61	-0.10 (-0.45 to 0.24)	0%	
Blinding of patients						0.14
Adequate	5	151	120	-0.46 (-0.70 to -0.21)	0%	
Inadequate or unclear	4	75	61	-0.10 (-0.45 to 0.24)	0%	

Table 2. Results of stratified analyses of function (*Continued*)

Use of analgesic cointerventions						0.95
Similar between groups	2	69	48	-0.33 (-0.70 to 0.05)	0%	
Not similar or unclear	7	157	133	-0.34 (-0.60 to -0.08)	15%	
Intention-to-treat analysis						0.76
Yes	2	40	42	-0.28 (-0.71 to 0.16)	0%	
No or unclear	7	186	139	-0.35 (-0.58 to -0.12)	5%	
Type of ES**						0.32
High frequency TENS	4	84	70	-0.18 (-0.50 to 0.14)	0%	
Burst TENS	0					
Modulation TENS	0					
Low frequency TENS	1	25	25	-0.88 (-1.46 to -0.30)	N/A	
Interferential current stimulation	3	40	34	-0.27 (-0.75 to 0.20)	0%	
Pulsed ES	2	77	52	-0.36 (-0.72 to -0.00)	0%	
Duration of ES per session						0.80‡
≤ 20 minutes	5	100	86	-0.29 (-0.69 to 0.11)	44%	

Table 2. Results of stratified analyses of function (*Continued*)

30 to 40 minutes	2	49	43	-0.37 (-0.79 to 0.04)	0%	
≥ 60 minutes	2	77	52	-0.36 (-0.72 to -0.00)	0%	
Number of sessions per week						0.32‡
≤ 3	4	75	61	-0.10 (-0.45 to 0.24)	0%	
4 to 6	3	74	68	-0.54 (-0.88 to -0.20)	2%	
≥ 7	2	77	52	-0.36 (-0.72 to -0.00)	0%	
Duration of ES per week						0.32‡
≤ 1 hour	4	75	61	-0.10 (-0.45 to 0.24)	0%	
> 1 to 5 hours	3	74	68	-0.54 (-0.88 to -0.20)	2%	
> 5 hours	2	77	52	-0.36 (-0.72 to -0.00)	0%	
Duration of treatment period						0.18
< 4 weeks	3	74	68	-0.54 (-0.88 to -0.20)	2%	
≥ 4 weeks	6	152	113	-0.23 (-0.47 to 0.02)	0%	

ES: electrostimulation; **Adedoyin 2005 contributed to two different strata: high-frequency TENS and interferential current stimulation; ‡ = P values from test for trend.

Other safety outcomes

Three trials (175 patients) contributed to the meta-analysis of patients experiencing any adverse event (Figure 8) and four trials (195 patients) to the meta-analysis of patients experiencing any serious adverse event (Figure 9). In general, there was no evidence to suggest that electrostimulation is unsafe, but 95% CIs were wide and results inconclusive.

Figure 8. Forest plot of 3 trials comparing patients experiencing any adverse event between any transcutaneous electrostimulation and control (sham or no intervention). Values on x-axis denote risks ratios. The risk ratio in one TENS trial could not be estimated because no adverse event occurred in either group. The plot is stratified according to type of electrostimulation.

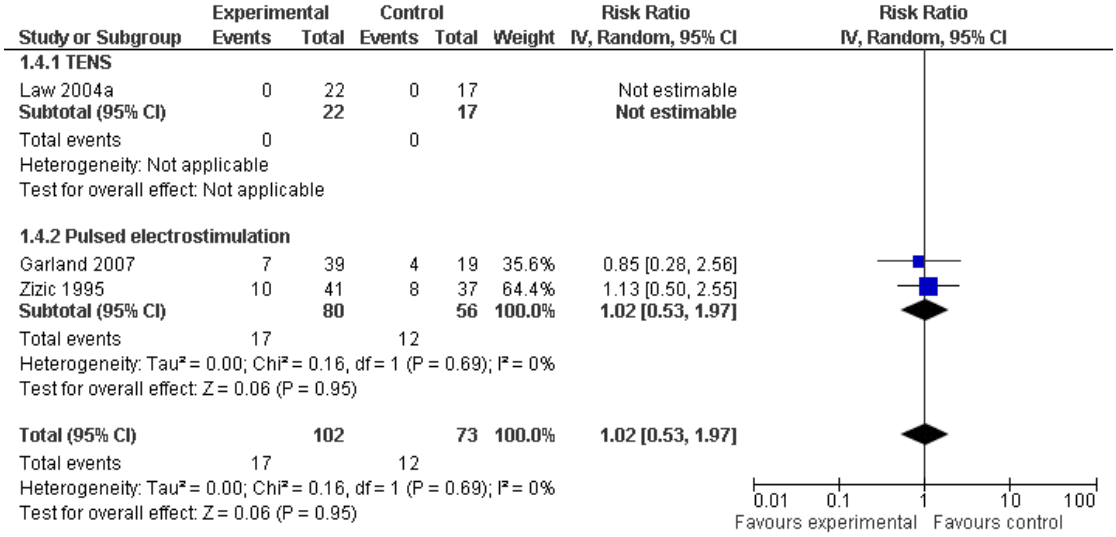
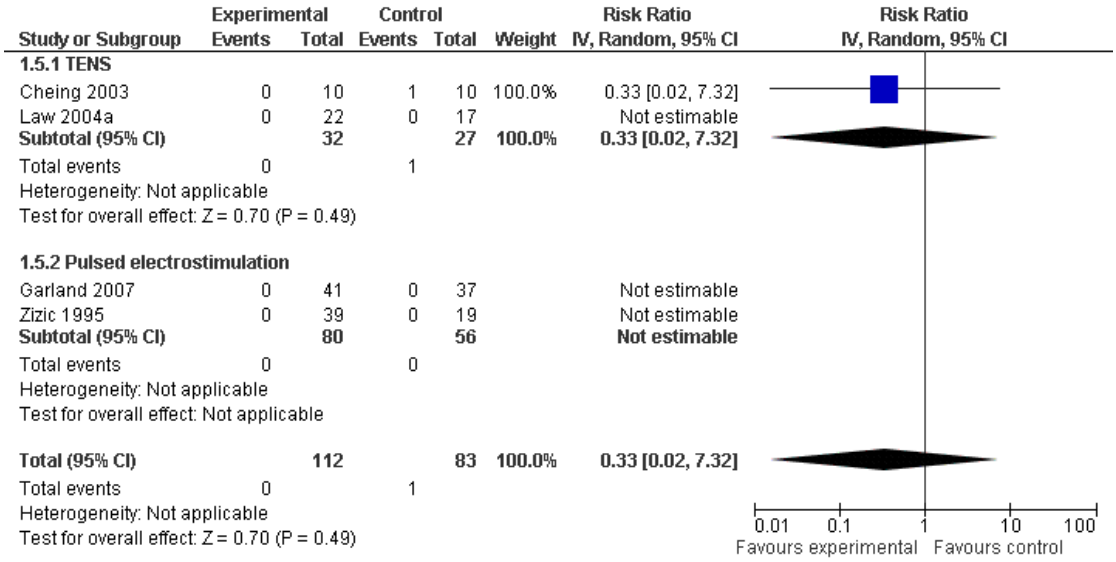


Figure 9. Forest plot of 4 trials comparing patients experiencing any serious adverse event between any transcutaneous electrostimulation and control (sham or no intervention). Values on x-axis denote risk ratios. Risk ratios could not be estimated in 3 trials, because no serious adverse event occurred in either group. The plot is stratified according to type of electrostimulation. Data relating to the 3 active intervention arms in Cheing 2003 were pooled.



DISCUSSION

Summary of main results

Our systematic review of trials comparing any type of transcutaneous electrostimulation with a sham or non-intervention control revealed a lack of adequately sized, methodologically sound and appropriately reported trials and a moderate to high degree of heterogeneity between trials, which made the interpretation of results difficult, particularly for joint pain as the primary therapeutic target of transcutaneous electrostimulation. In an attempt to minimise biases associated with small trials of questionable quality, we used meta-regression to predict effects of transcutaneous electrostimulation on pain and found the predicted effect sizes for pain negligibly small. The rates of withdrawals or drop-outs due to adverse events were comparable in experimental and control groups, but 95% CIs were wide and therefore inconclusive.

Quality of the evidence

An inspection of funnel plots and a formal analysis of asymmetry indicated asymmetry for knee pain, but not for function, which suggested the presence of biases associated with small sample size particularly when estimating the effects of electrostimulation on knee pain. Asymmetrical funnel plots should be seen not only as an indication of publication bias, but as a generic tool for examination of small study effects: the tendency for the smaller studies to show larger treatment effects, possibly due to a combination of publication bias, selective reporting of outcomes and methodological problems particularly in small trials (Nuesch 2009a; Sterne 2000). If reporting is inadequate, as was the case in our systematic review, then the standard error as a proxy for study size may be a more precise measure of trial quality than formal assessments of methodological quality. When modelling effects expected in trials as large as the largest trial included in our systematic review, we found effects on pain near null -0.07 (95% CI -0.46 to 0.32), which were clearly smaller than the pooled SMD actually found for pain in the meta-analysis -0.86 (95% CI -1.23 to -0.49). The effect of electrostimulation on function was small, but potentially clinically relevant, and the accumulated evidence appeared less affected by biases associated with small sample size.

The methodological quality and the quality of reporting was poor. Insufficient information was noted in several randomised controlled trials about the treatment assignment procedure and concealment of allocation. Primary outcomes were specified in only three trials. Although several studies reported blinding of patients, complete blinding is difficult to achieve due to the sensory differences between treatment and placebo, as well as unintended communication between patient and evaluator (Deyo 1990). Only Grimmer 1992 and Bal 2007 mentioned the inclusion of patients to be restricted to those without prior TENS experience; another two trials were likely to have achieved adequate blinding of patients with currents below the sensory threshold used in the experimental group, which were likely to be indistinguishable from the sham intervention also for patients with treatment experience (Garland 2007, Zizic 1995). The majority of papers did not provide adequate information regarding withdrawals, drop-outs and losses to follow up, nor indicated whether patients with incomplete clinical data were included in the data analysis. Several trials omitted to describe adverse events, which is of concern.

Potential biases in the review process

Our review is based on a broad literature search, and it seems unlikely that we missed relevant trials. Trial selection and data extraction, including quality assessment, were done independently by two authors to minimise bias and transcription errors. Components used for quality assessment are validated and reported to be associated with bias (Jüni 2001; Wood 2008).

As with any systematic review, our study is limited by the quality of included trials. As indicated above, trials generally suffered from poor methodological quality, inadequate reporting and small sample size. Some trials (Cheing 2003; Defrin 2005; Law 2004a) showed unrealistically large SMDs of twice to three times the magnitude of what would be expected for total joint replacement (Jüni 2006). Including these trials in the meta-analysis is likely to result in an overestimation of the benefits of transcutaneous electrostimulation.

Agreements and disagreements with other studies or reviews

Interestingly, there are nearly as many systematic reviews and meta-analyses on transcutaneous electrostimulation in osteoarthritis as randomised trials. Here, we will focus mainly on the similarities and differences between ours and the previous version of this review (Osiri 2000), which included seven transcutaneous electrical nerve stimulation (TENS) trials. We updated the search and used broader selection criteria, which resulted in 14 additional trials; 11 trials used TENS as the experimental treatment, four interferential current stimulation, one both TENS and interferential current stimulation, and two pulsed electrostimulation. As in the review of Osiri 2000, both parallel group and cross-over RCTs were included. For the cross-over studies, we only collected data from the first intervention phase in order to eliminate carry-over effects, whereas Osiri and colleagues included pooled data over all phases. We excluded three previously included cross-over trials, because the investigators were unable to provide data from the first phase only. In this update, we performed a more detailed quality assessment of component trials, followed by a detailed exploration of sources of variation between trials, including concealment of allocation, blinding, intention-to-treat analysis, characteristics of

electrostimulation, and the investigation of funnel plots. To analyse continuous data, Osiri and colleagues used weighted mean differences or SMDs of the change from baseline scores, whereas we used SMDs of end of treatment scores and based our conclusions on treatment effects on pain predicted in uni-variable meta-regression models by using the standard error as the explanatory variable. In addition, fixed-effect models were used in the previous version unless there was statistically significant heterogeneity between trials based on χ^2 testing. Model selection based on the mechanistic application of heterogeneity tests should be avoided, however. Here, we used random-effects models, which will generally be more conservative in terms of the estimated precision, but will be more affected by small study effects than a fixed-effect model, which makes an exploration of sources of variation, including different types of bias, mandatory. Results from the previous and current versions are therefore not directly comparable. Nevertheless, pooled SMDs for pain were favourable in our and the previous review (Osiri 2000), with us reporting a pooled SMD of -0.86 (95% CI -1.23 to -0.49), whereas Osiri 2000 reported a SMD of -0.45 (95% CI -0.70 to -0.19), with confidence intervals overlapping widely. Although both Osiri and we acknowledge the risk of bias in summary estimates, Osiri concluded that transcutaneous electrostimulation is "shown to be effective in pain control over placebo". We disagree with these conclusions: when modelling effects expected in trials as large as the largest trial included, we found the SMD of pain near null and clinically irrelevant (-0.07, 95% CI -0.46 to 0.32). Osiri 2000 recorded function separately for the outcomes 'stiffness of the knee', '50-foot walking time', 'quadriceps muscle strength' and 'knee flection' with only one trial contributing to each of the categories. We choose a different approach, using a hierarchy developed to minimise the impact of selective reporting of outcomes and to allow for a synthesis of evidence across different studies using divergent definitions of function. Our effect sizes and conclusion concerning function are less favourable compared to those made by Osiri 2000. In this version, we also summarised safety data and found no evidence to suggest that electrostimulation is unsafe. Finally, unlike Osiri 2000, we also included trials of interferential current stimulation and pulsed electrostimulation. One of the two trials of pulsed electrostimulation (Zizic 1995) is covered in another Cochrane Review by Hulme 2002 on electromagnetic fields, even though the device used (BioniCare BIO-1000) does not generate electromagnetic fields, but electric currents (Regence Medical Policy 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Despite more than 20 years of clinical research, there is a lack of adequate evidence to support the use of any type of transcutaneous electrostimulation in patients with knee osteoarthritis. The effects on both knee pain and function are potentially clinically relevant and deserve further clinical evaluation.

Implications for research

The current systematic review is inconclusive, hampered by the inclusion of only small trials of questionable quality (Nuesch 2009a). Adequately sized randomised parallel-group trials in about 2 x 100 patients with knee osteoarthritis are necessary to determine whether a specific type of transcutaneous electrostimulation is indeed associated with a clinically relevant benefit on pain. A sample size of 2 x 100 patients will yield more than 80% power to detect a small to moderate SMD of -0.40 at a two-sided P of 0.05, which corresponds to a difference of 1 cm on a 10 cm visual analogue scale (VAS) between experimental and control intervention. The trials should enrol patients without prior experience of any type of transcutaneous electrostimulation or evaluate success of blinding at the end of trial, use adequate concealment of allocation, experimental and sham interventions that are close to indistinguishable and an intention-to-treat analysis. Transcutaneous electrical nerve stimulation (TENS) devices are marketed as small, inexpensive, easy-to-use home units, but in the majority of trials TENS was administered by a therapist in a practice or hospital setting. Future research may focus on the effectiveness of self-administered TENS, with accurate recording of the duration of electrostimulation per day to assess compliance and enable the exploration of possible dose-effect relationships.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adedoyin 2002

Methods	Quasi-randomised trial using alternation for the allocation of patients 2-arm parallel group design Trial duration: 4 weeks No power calculation reported
Participants	30 patients randomised 30 patients with knee OA reported at baseline Study joints: 30 knees Number of females: 20 of 30 (67%) Average age: 59 years Average BMI: 28 kg/m^2
Interventions	Experimental intervention: interferential current stimulation, dietary advice and exercise, twice per week Control intervention: Sham interferential current stimulation, dietary advice and exercise, twice per week Duration of treatment period: 4 weeks Analgesics not allowed Device: Enraf-Nonius Endomed 5921 (4 pole) Self-administered: no Waveform: interferential Pulse width: not applicable Pulse frequency: amplitude-modulated frequency of 100 Hz for 15 min (beat frequency), 80 Hz for last 5 min (beat frequency) Amplitude: above sensory threshold, up to appreciable sensation Duration of stimulation per session: 20 minutes Electrodes: 4 electrodes covered with padding Placement: 2 latero-medial, 2 antero-posterior
Outcomes	Extracted pain outcome: global pain after 4 weeks, described as "Pain perception (VAS)" No function outcome reported Primary outcome: global pain (VAS)
Notes	All subjects from black Nigerian population

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Alternation

Adedoyin 2002 (*Continued*)

Allocation concealment?	No	Alternation
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes
Adequate blinding of patients?	Yes	Sham device: identical in appearance, not increasing intensity, flash light on, patient in position unable to read level of intensity
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Yes	-
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable, no function outcome reported
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Adedoyin 2005

Methods	Randomised controlled trial 3-arm parallel group design Trial duration: 4 weeks Power calculation reported
Participants	51 patients randomised 46 patients with knee OA reported at baseline Study joints: 46 knees Number of females: 28 of 46 (61%) Average age: 55 years Average BMI: 28 kg/m2
Interventions	*Comparison 1* Experimental intervention: TENS and exercise twice per week Control intervention: exercise, twice per week *Comparison 2* Experimental intervention: interferential current stimulation and exercise, twice per week Control intervention: exercise, twice per week Duration of treatment period: 4 weeks Analgesics not allowed, patients confirmed not to take analgesics TENS Device: Endomed 5921D

Adedoyin 2005 (*Continued*)

	Self-administered: no Waveform: not reported Pulse width: 200 ms Pulse frequency: 80 Hz Amplitude: above sensory threshold, strong but comfortable Duration of stimulation per session: 20 minutes Electrodes: 2 electrodes 8 x 6 cm Placement: Each side of affected knee joint, aligned longitudinally along length of limb Interferential Current Stimulation Device: Endomed 5921D (2 pole) Waveform: interferential Pulse width: not applicable Pulse frequency: 80 Hz (beat) Amplitude: above sensory threshold: strong but comfortable, strong tingling sensation without muscle contraction Duration of stimulation per session: 20 minutes Electrodes: 2 electrodes 8 x 6 cm Placement: each side of affected knee joint, aligned longitudinally along length of limb
Outcomes	Extracted pain outcome: pain on activities other than walking after 4 weeks, described as "Pain recorded while standing (10-point pain rating scale with 0 "no pain", 5 "moderate pain" and 10 "worst pain imaginable")" Extracted function outcome: WOMAC global scale after 4 weeks (Likert) No primary outcome reported
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes
Adequate blinding of patients?	No	No sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	15 out of 15 (100%) in TENS group, 16 out of 19 (84%) in interferential current stimulation group, 15 out of 17 (88%) in control group analysed

Adedoyin 2005 (*Continued*)

Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Bal 2007

Methods	Quasi-randomised single centre controlled trial with allocation according to hospital registration number 2-arm parallel group design Trial duration: 13 weeks No power calculation reported
Participants	56 patients randomised 56 patients with knee OA reported at baseline Study joints: 56 knees Number of females: 50 of 56 (89%) Average age: 57 years Average BMI: 31 kg/m2 Average disease duration: 2 years
Interventions	Experimental intervention: TENS and infra-red therapy, 5 times per week Control intervention: sham TENS and infra-red therapy, 5 times per week Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and the intake was assessed Device: PlusMED 1-904 Self-administered: no Waveform: not reported Pulse width: 140 μsec Pulse frequency: 80 Hz Amplitude: above sensory threshold, not up to maximum tolerance, no muscle contractions observed* Duration of stimulation per session: 40 minutes Electrodes: 4, type unclear Placement: acupuncture points: ST36, GB34, SP10, SP9, ST34
Outcomes	Extracted pain outcome: WOMAC pain subscore after 13 weeks (Likert) Extracted function outcome: WOMAC disability subscore after 13 weeks (Likert) No primary outcome reported

Bal 2007 (*Continued*)

Notes	Article in Turkish, outcome assessment done by AR and RS assisted by a native Turkish researcher. Serpil Bal verified all extracted data. *as indicated by Serpil Bal in personal communication.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	The published report only stated that there was a random allocation of patients to comparison groups. In personal communication, investigator Serpil Bal stated that the patients were allocated according to last digit of their hospital registration number. Patients with even numbers were assigned to TENS group, patients with odd numbers to a sham intervention.
Allocation concealment?	No	No, the same investigator responsible of randomisation was giving interventions, as indicated by Serpil Bal in personal communication
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes, we have been unable to sort out this item with investigator Serpil Bal
Adequate blinding of patients?	Yes	Trial is described as single blind study using sham device PlusMED 1-904, indistinguishable from real TENS unit. Sham device had broken leads, no current passed but flashing light was on. None of the patients had prior experience with TENS.
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Yes	All subjects were available for end of treatment measurements, as indicated by Serpil Bal in personal communication
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Yes	All subjects were available for end of treatment measurements, as indicated by Serpil Bal in personal communication
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Cetin 2008

Methods	Randomised controlled trial 5-arm parallel group design Trial duration: 8 weeks No power calculation reported
Participants	100 patients randomised 100 patients with knee OA reported at baseline Study joints: 100 knees Number of females: 100 of 100 (100%) Average age: 60 years Average BMI: 28 kg/m2
Interventions	Experimental intervention: TENS + hot packs + isokinetic exercise, 3 times per week Control intervention: hot packs + isokinetic exercise, 3 times per week Duration of treatment period: 8 weeks Analgesics allowed, unclear whether intake was similar between groups Device: MED911 Self-administered: no Waveform: not reported Puls width: 60 msecs Pulse frequency: 60-100 Hz Amplitude: above sensory threshold, increased to point of seeing no contraction, while patient felt comfortable Duration of stimulation per session: 20 minutes Electrodes: not reported Electrode placement: around painful areas
Outcomes	Extracted pain outcome: pain on walking after 8 weeks, described as "Knee pain severity after a 50-m walk (VAS)" Extracted function outcome: Lequesne OA index global score after 8 weeks (Likert) No primary outcome reported
Notes	Only 2 arms qualified for inclusion in this review

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes

Cetin 2008 (*Continued*)

Adequate blinding of patients?	No	No sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Unclear	No information provided
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	No information provided
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Cheing 2002

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 8 weeks Randomisation stratified according to age, gender, BMI No power calculation reported
Participants	66 patients randomised 62 patients with knee OA reported at baseline Study joints: 62 knees Number of females: 53 of 62 (85%) Average age: 64 years Average BMI: 28 kg/m^2
Interventions	*Comparison 1* Experimental intervention: 60 min TENS, 5 times per week Control intervention: sham TENS, 5 times per week *Comparison 2* Experimental intervention: TENS plus exercise, 5 times per week Control intervention: exercise alone, 5 times per week Duration of treatment period: 4 weeks Analgesics allowed, unclear whether intake was similar between groups Device: MAXIMA III (dual channel) Self-administered: unclear, most likely not Waveform: square Pulse width: 140 μsec Pulse frequency: 80 Hz Amplitude: above sensory threshold, tingling sensation, 3 to 4 times above sensory threshold

Cheing 2002 (*Continued*)

	Duration of stimulation per session: 60 minutes Electrodes: 4 electrodes of 4 x 4 cm Placement: at acupuncture points: ST35, SP9, GB34, extra 31,32 (one electrode covering both extra 32 and ST35)
Outcomes	Extracted pain outcome: global pain after 8 weeks, described as "Intensity of subjective pain sensation (Baseline score on 0-10 cm VAS was standardised to be 100% in each of the groups. Follow up values were expressed as mean decrease in % from baseline)". No function outcome reported No primary outcome reported
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes
Adequate blinding of patients?	Yes	Comparison 1: Yes, sham device identical in appearance to real TENS unit, no current passed but indicator light was lit up Comparison 2: No, no sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	Comparison 1: 16 out of 16 (100%) randomised to experimental and 16 out of 18 (89%) randomised to control group were analysed Comparison 2: 15 out of 17 (88%) randomised to experimental and 15 out of 15 (100%) randomised to control group were analysed
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Cheing 2003

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 4 weeks Randomisation stratified according to gender No power calculation reported
Participants	40 patients randomised 38 patients with knee OA reported at baseline Study joints: 38 knees Number of females: 34 of 38 (89%) Average age: 66 years
Interventions	Experimental intervention: 20 min TENS in group 1, 40 min TENS in group 2, 60 min TENS in group 4, 5 times per week Control intervention: sham TENS, 5 times per week Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and whether intake was similar between groups Device: ITO 120Z TENS (dual channel) Self-administered: no Waveform: not reported Pulse width: 200 μsec Pulse frequency: 100 Hz Amplitude: above sensory threshold, strong but comfortable Duration of stimulation per session: 20 minutes Electrodes: 4 of 2 x 3 cm rubber electrodes Placement: 4 acupuncture points extra 31,32, ST35, GB34, SP9
Outcomes	Extracted pain outcome: pain on walking after 4 weeks, described as "pain during walking (VAS)" No function outcome reported No primary outcome reported
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes

Cheing 2003 (*Continued*)

Adequate blinding of patients?	Yes	Sham device: electronic circuit disconnected, no current passed, but indicator light on
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	30 out of 30 (100%) randomised to experimental and 8 out of 10 (80%) randomised to control group were analysed
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Defrin 2005

Methods	Randomised controlled trial 6-arm parallel group design Trial duration: 4 weeks No power calculation reported
Participants	62 patients randomised 62 patients with knee OA reported at baseline Study joints: 62 knees Average age: 67 years
Interventions	Experimental intervention: noxious adjusted interferential current stimulation in group 1, noxious unadjusted interferential current stimulation in group 2, innocuous adjusted interferential current stimulation in group 3, innocuous unadjusted interferential current stimulation in group 4, 3 times per week Control intervention: sham interferential current stimulation, 3 times per week Duration of treatment period: 4 weeks Analgesics allowed, unclear whether intake was similar between groups. Device: Uniphy: Phyaction electrical stimulator Self-administered: no Waveform: interferential Pulse width: not applicable Pulse frequency: 30 to 60 Hz (beat) Amplitude: above sensory threshold, 2 groups 30% above pain threshold; 2 groups 30% below pain threshold Duration of stimulation per session: 20 minutes Electrodes: 2 of 8 x 6 cm wet sponge electrodes Placement: medial and lateral aspects of the knee, 2 cm from outer margins of patella

Defrin 2005 (*Continued*)

Outcomes	Extracted pain outcome: global pain after 4 weeks, described as "chronic pain intensity (VAS)" No function outcome reported No primary outcome reported
Notes	1 out of 6 trial arms, the no-intervention control group was excluded in the review

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes
Adequate blinding of patients?	Unclear	Use of sham device: Uniphy-Phyaction electrical stimulator, however the device described as shut-off
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Unclear	No information provided
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Fargas-Babjak 1989

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 13 weeks No power calculation reported
Participants	56 patients randomised 56 patients with knee OA reported at baseline Study joints: 56 joints, most likely > 75% knees

Fargas-Babjak 1989 (*Continued*)

	Average age; gender, BMI: not reported
Interventions	Experimental intervention: burst TENS, twice per day Control intervention: sham TENS, twice per day Duration of treatment period: 6 weeks Analgesics allowed, but change of dosage prohibited. Unclear whether analgesics were assessed and whether intake was similar between groups. Device: Codetron Self-administered: yes Waveform: square Pulse width: 1000 μsec Pulse frequency: 200 Hz, train length of 125 ms, repetition frequency of 4 Hz (25 pulses per train) Amplitude: above sensory threshold, highest intensity that could be tolerated without inducing frank pain Duration of stimulation per session: 30 minutes Electrodes: 7 carbon rubber (self-adhesive) Karaya Pads electrodes of 2 x 3 cm Placement: 10 acupuncture points: GV14, GV4, GB30, GB34, SP13, B1 60, ST36, B1 40, SP9, LI4 and 3 extra tender points
Outcomes	Extracted pain outcome: global pain after 13 weeks described as "Pain improvement (percentage pain improvement based on VAS)" No function outcome reported No primary outcome reported
Notes	*Investigators named their intervention AL-TENS, but we coded it burst TENS in the analyses

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	No	Quote: "Full details of this (Percent Improvement Pain Scale) are reported elsewhere". Investigators however failed to provide reference.
Adequate blinding of patients?	Yes	Use of sham device: Codetron, identical in appearance, set at frequency of 0.2 Hz with a threshold electrical stimulus of 0.5 mA, which caused a sensation on the skin but failed causing the deep muscle afferent stimulation

Fargas-Babjak 1989 (*Continued*)

Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	56 patients randomised but only 19 analysed in the experimental, and 18 analysed in the control group
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	No	Sponsor: Electronic Health Machines
Funding by non-profit organisation?	Yes	NRC grant no: 689

Garland 2007

Methods	Randomised multicentre controlled trial 2-arm parallel group design Number of participating centres: 3 Trial duration: 12 weeks Randomisation stratified according to study site No power calculation reported
Participants	100 patients randomised 58 patients with knee OA reported at baseline; 41 out of 58 candidates for total knee arthroplasty Study joints: 58 knees Number of females: 38 of 58 (66%) Average age: 66 Disease duration: 8.4 years
Interventions	Experimental intervention: pulsed electrical stimulation Control intervention: sham intervention Duration of treatment period: 12 weeks Analgesics allowed and intake assessed, but unclear whether intake was similar. Device: BIO-1000 Self-administered: yes Waveform: unclear Pulse width: unclear Pulse frequency: 100 Hz Amplitude: below sensory threshold, initial increase of amplitude up to 12 Volt until a tingling sensation was felt then reduction of the amplitude until this sensation disappeared Duration of stimulation per session: 8.2 hours in active group, 7.8 hours in sham group (mean daily application time) Electrodes: flexible electrodes embedded in garment, type not reported

Garland 2007 (*Continued*)

	Electrode placement: negative electrode at patella, positive over anterior distal thigh
Outcomes	Extracted pain outcome: global pain after 12 weeks, described as "Considering your pain and symptoms in your study joint how are you doing today? (VAS)" Extracted function outcome: WOMAC disability subscore after 12 weeks (VAS) No primary outcome reported
Notes	*Due to major protocol violations, all 42 randomised patient of one site were excluded by Garland et al

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Yes	Central randomisation
Free of selective reporting?	Unclear	Quote: "Total WOMAC scores were not a defined outcome in the protocol, but are shown in Tables II(a)-(d)."
Adequate blinding of patients?	Yes	Use of sham device: BIO-1000, indistinguishable from active device, with automatic shut-off as soon as amplitude is reduced (all patients were instructed to reduce intensity just below perception level). Further adjustments required all devices to be restarted.
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	Due to major protocol violations, all 42 randomised patient of 1 site were excluded by original authors. From the other site, all patients randomised were included in the analysis.
Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above
Funding by commercial organisation avoided?	No	Sponsor: BioniCare Medical Technologies
Funding by non-profit organisation?	Unclear	No information provided

Grimmer 1992

Methods	Randomised controlled trial 3-arm parallel group design Trial duration: 1 day No power calculation reported
Participants	60 patients randomised 60 patients with knee OA reported at baseline Study joints: 60 knees Number of females: 37 of 60 (62%) Average age: 66 years
Interventions	Experimental intervention: high frequency TENS, once only in group 1, burst TENS, once only in group 2 Control intervention: sham TENS, once only Duration of treatment period: 1 day Analgesics not allowed Device: Medtronic Neuromed Selectra (dual channel) Self-administered: no Waveform: unclear Pulse width: unclear Pulse frequency: 80 Hz in group 1, 3 Hz trains of 7 80 Hz pulses in group 2 Amplitude: above sensory threshold, strong tolerable tingling paraesthesia Duration of stimulation per session: 30 minutes Electrodes: 4 carbon rubber silicone electrodes, 2 x 3 cm Placement: 4 acupuncture points around the knee: medial (SP9), lateral (GB33), posterior (UB40), anterior (SP10)
Outcomes	Extracted pain outcome: global pain immediately after first and only application, described as "Immediate pain relief (VAS)" No function outcome reported No primary outcome reported
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomly allocated (by dice) into three groups of 20"
Allocation concealment?	Yes	By a person independent of the study
Free of selective reporting?	Unclear	Insufficient information provided; no access to study protocol

Grimmer 1992 (*Continued*)

Adequate blinding of patients?	Yes	Sham device: Medtronic Neuromed Selectra, with non-functioning leads. Patient were told that a very high frequency current was being tested and that no skin sensation would be felt.
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Yes	Degrees of freedom reported indicate that all randomised patients were included in the analysis
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Itoh 2008

Methods	Randomised controlled trial 2 x 2 factorial design Trial duration: 10 weeks No power calculation reported
Participants	32 patients randomised 32 patients with knee OA reported at baseline Study joints: 32 knees Number of females: 21 of 32 (66%)
Interventions	Experimental intervention: interferential current stimulation*, once per week Control intervention: no intervention, optional use of poultice 16 out of 32 patients (50%) allocated to acupuncture using a factorial design; no evidence for an interaction between treatments Duration of treatment period: 5 weeks Analgesics allowed and intake assessed, but unclear whether intake was similar. Device: HV-F3000 (single channel, 2 pole) Self-administered: no Waveform: sinusoidal Pulse width: not applicable Pulse frequency: amplitude-modulated frequency of 122 Hz (beat frequency) Amplitude: above sensory threshold, up to a tingling sensation, 2 to 3 times above sensory threshold Duration of stimulation per session: 15 minutes Placement: site of tenderness and opposite site Electrodes: 2 disposable electrodes different in size, 809 mm^2 and 5688 mm^2

Outcomes	Extracted pain outcome: global pain after 10 weeks, described as "Pain intensity (VAS)" Extracted function outcome: WOMAC global scale after 10 weeks (VAS) Primary outcomes: pain intensity, WOMAC global scale
Notes	*The investigators used the label TENS in their report, but from their description of the intervention it was clear that interferential current stimulation was applied

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated block randomisation. Quote "According to a block randomised allocation table (generated by Sample Size, version 2.0, Int), the enrolled patients were allocated to (1) the control (CT) group, (2) the acupuncture (ACP) group, (3) the transcutaneous electrical nerve stimulation (TENS) group or (4) the acupuncture and TENS (A&T) group."
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Insufficient information provided, no access to study protocol
Adequate blinding of patients?	No	No sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	12 out of 16 (75%) randomised to experimental and 12 out of 16 (75%) randomised to control group were analysed
Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Law 2004

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 4 weeks No power calculation reported
Participants	36 patients randomised 36 patients with knee OA reported at baseline Study joints: 48 knees* Number of females: 35 of 36 (97%) Average age: 82 years
Interventions	Experimental intervention: 2 Hz TENS in group 1, 100 Hz TENS in group 2, modulation TENS with alternations between 2 to 100 Hz in group 3, 5 times per week in all groups Control intervention: sham TENS, 5 times per week Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and whether intake was similar between groups Device: Han Acupoint Nerve Stimulation LH204H Self-administered: no Waveform: unclear Pulse width and frequency: 576 μsec and 2 Hz in group 1, 200 μsec and 100 Hz in group 2, 576/200 μsec and 2/100 Hz alternation in group 3 Amplitude: above sensory threshold, up to comfortable level, range 25 to 35 mA Duration of stimulation per session: 40 minutes Electrodes: 4 rubber electrodes of 4.5 x 3.8 cm Placement: 4 acupuncture points: ST35, LE4, SP9, GB34
Outcomes	Extracted pain outcome: pain on walking after 4 weeks, described as "intensity of pain felt while walking (VAS)" No function outcome reported No primary outcome reported
Notes	Outcome data were reported on knee level.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Randomization was carried out by drawing lots from the randomization envelope."
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Insufficient information provided; no access to study protocol

Law 2004 (*Continued*)

Adequate blinding of patients?	Yes	Use of sham device: identical in appearance, internal circuit disconnected, no current passed, indicator light on, digital display of intensity control functioned normally. Quote: "Only therapists who administered treatment to the subjects knew the group allocation, while the subjects and the assessor were not given this information."
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	In total, 3 patients dropped out and were excluded from analysis, as indicated by Gladys Cheing and Pearl Law in personal communication
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Law 2004a

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 2 weeks Unstratified randomisation Multicentre trial with 2 centres No power calculation reported
Participants	39 patients randomised 39 patients with knee OA reported at baseline Study joints: 39 knees Number of females: 37 of 39 (95%) Average age: 75 years Average BMI: 27 kg/m2 Average disease duration: 7.6 years
Interventions	Experimental intervention: TENS, 5 times per week Control intervention: sham TENS, 5 times per week Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and whether intake was similar between groups Device: ITO model 120Z (dual channel) Self-administered: no Waveform: unclear Pulse width: 200 μsec

Law 2004a (*Continued*)

	Pulse frequency: 100 Hz Amplitude: above sensory threshold, up to a comfortable level, range 25-35 mA Duration of stimulation per session: 40 minutes Electrodes: 4 rubber electrodes, 4.5 x 3.8 cm^2 Placement: acupuncture points: ST35, LE4, SP9, GB34
Outcomes	Extracted pain outcome: pain on walking after 2 weeks, described as "intensity of pain felt while walking (VAS)"** Extracted function outcome: walking disability after 2 weeks, described as "Timed-Up-and-Go test over 3 meters (seconds)" No primary outcome reported
Notes	**Only baseline values reported in the report. Contact established with investigators Law and Cheing, who provided end of treatment and follow-up data.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "'by drawing lots from the randomization envelope without replacement"
Allocation concealment?	Unclear	Quote : "(...) carried out by physiotherapists who performed the treatment"
Free of selective reporting?	No	No results reported for some outcomes mentioned in the methods section, including pain intensity on VAS
Adequate blinding of patients?	Yes	Use of sham device: ITO model 120Z, no current delivered but flashing light on. Quote: "The assessors and subjects were blind to the group allocation. All subjects were told that when the indicator light of the TENS was blinking, it meant the machine was working properly. They might or might not feel any tingling sensation during treatment because the intensity of the current was small."
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	In total, 3 patients dropped out and were excluded from analysis, as indicated by Gladys Cheing and Pearl Law in personal communication
Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above

Law 2004a (*Continued*)

Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Ng 2003

Methods	Randomised controlled trial 3-arm parallel group design Trial duration: 4 weeks Unstratified randomisation No power calculation reported
Participants	24 patients randomised 24 patients with knee OA reported at baseline Study joints: 24 knees Number of females: 23 of 24 (96%) Average age: 85 years
Interventions	Experimental intervention: TENS, 4 times per week, with a total of 8 applications and educational pamphlet Control intervention: educational pamphlet Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and whether intake was similar between groups Device: ITO model F-2 (dual channel) Self-administered: no Waveform: unclear Pulse width: 200 μsec Pulse frequency: 2 Hz Amplitude: above sensory threshold, until strong, tolerable, stroking sensation, preferably evoking phasic muscle contraction Duration of stimulation per session: 20 minutes Electrode placement: acupuncture points ST35, EX-LE-4 Electrodes: 50 x 35 mm^2
Outcomes	Extracted pain outcome: global pain after 4 weeks, described as "pain (Numeric rating scale (NRS))" No function outcome reported No primary outcome reported
Notes	2 out of 3 trial arms qualified for inclusion in this review

Risk of bias

Ng 2003 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Drawing lots. Quote: "Subjects were randomly assigned by drawing a piece of paper that designated each person to the EA, TENS, and control groups"
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Yes	Quote: "In each evaluation session, three outcome measures were collected." The authors present results of all these 3 outcomes.
Adequate blinding of patients?	No	No sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Unclear	No information provided
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Quirk 1985

Methods	Randomised controlled trial 3-arm parallel group design* Trial duration: 26 weeks No power calculation reported
Participants	38 patients randomised 38 patients with knee OA reported at baseline Study joints: 38 knees Number of females: 29 of 38 (76%) Average age: 63 years
Interventions	Experimental intervention: interferential current + exercise, interferential current stimulation: 3 times per week, exercise twice daily Control intervention: exercise twice daily Duration of treatment period: 4 weeks Analgesics allowed, unclear whether intake was similar between groups

Quirk 1985 (*Continued*)

	Device: Endomed 433 and Vacutron 423 (unclear whether 2 or 4 pole) Self-administered: no Waveform: interferential Pulse width: not applicable Pulse frequency: 0 to 100 Hz 10 minutes, 130 Hz last 5 minutes Amplitude: not reported Duration of stimulation per session: 15 minutes Electrodes: suction electrodes Placement: not reported
Outcomes	Extracted pain outcome: other after 26 weeks, described as "Pain composite score with items rest, post-exercise and night pain (approach unclear; either VAS or verbal scoring technique modified after Newland)"** Extracted function outcome: other algofunctional scale after 26 weeks, described as "Overall clinical condition scale developed by authors, which was based on 3 items for pain; rest-, post-exercise-, night pain and 3 for function; gait, method of climbing stairs and using walking aids (most likely Likert)". No primary outcome reported
Notes	*1 trial arm, in which shortwave diathermy was given, was excluded, **only baseline values with standard error and P values for change from baseline per group reported. No contact could be established with the investigators.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	No	No results reported for some outcomes mentioned in the methods section, including maximum knee girth
Adequate blinding of patients?	No	No sham intervention
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	Yes	Quote: "All patients completed their therapy and the first two assessments (baseline and end of treatment), while 92% completed the final assessment (3-6 months after treatment)"
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Yes	See above

Quirk 1985 (*Continued*)

Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Smith 1983

Methods	Randomised sham controlled trial 2-arm parallel group design Trial duration: 8 weeks Randomisation stratified according to gender Multicentre trial with 2 centres No power calculation reported
Participants	32 patients randomised 30 patients with knee OA reported at baseline Study joints: 30 knees Number of females: 20 of 30 (67%) Average age: 68 years
Interventions	Experimental intervention: TENS, twice per week* Control intervention: sham TENS, twice per week* Duration of treatment period: 4 weeks Analgesics intake assessed and found to be similar between groups Device: RDG Tiger Pulse Self-administered: no Waveform: square Pulse width: 80 μsec Pulse frequency: 32 to 50 Hz Amplitude: above sensory threshold, adjusted up to a comfortable tingling sensation Duration of stimulation per session: 20 minutes Electrodes: 4 Lec Tec pads applied with electrode jelly Placement: tender knee points or acupuncture points (SP9, xiyan and UB40)
Outcomes	Extracted pain outcome: global pain after 8 weeks, described as "Weekly pain score derived from daily pain recording (linear 7-point scale)"** No function outcome reported No primary outcome reported
Notes	*Preceded by 1 'standard' week without any treatment, **No pain outcome data presented, investigators were contacted, but we did not receive any reply. This study only contributed in safety analysis.
Risk of bias	

Smith 1983 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated. Quote: "(...) assigned by random computer programme and effected by using sealed envelopes containing cards which defined the treatment (...)".
Allocation concealment?	Unclear	Sealed assignment envelopes, but unclear whether these were opaque and sequential
Free of selective reporting?	No	No results reported for some outcomes mentioned in the methods section, including sleep disturbance
Adequate blinding of patients?	Yes	Use of sham device: RDG Tiger Pulse with broken electrode connection at jack point, no current passed but flashing light on. Quote: "Exactly the same procedure were followed for both the treatment and control groups".
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	15 out of 16 (0.94) randomised to experimental and 15 out of 16 (0.94) randomised to control group were analysed
Incomplete outcome reporting: intention-to-treat analysis performed? Function	Unclear	Not applicable
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Yurtkuran 1999

Methods	Randomised controlled trial 4-arm parallel group design Trial duration: 2 weeks No power calculation reported
Participants	100 patients randomised, 25 per group 100 patients with knee OA reported at baseline Study joints: 100 knees Number of females: 91 of 100 (91%) Average age: 58 years

Yurtkuran 1999 (*Continued*)

Interventions	Experimental intervention: TENS, 5 times per week Control intervention: sham TENS, 5 times per week Duration of treatment period: 2 weeks Unclear whether analgesics were allowed and whether intake was similar between groups Device: MEA-TENS (dual channel) Self-administered: no Waveform: rectangular Pulse width: 1000 μsec Pulse frequency: 4 Hz* Amplitude: above sensory threshold, up to muscle contraction, just below pain tolerance threshold Duration of stimulation per session: 20 minutes Electrodes: 4 small MEA rubber electrodes Placement: 4 acupuncture points SP-9, GB-34, ST-34, ST-35
Outcomes	Extracted pain outcome: global pain after 2 weeks described as "Overall present pain intensity at rest (Likert)" Extracted function outcome: walking disability after 2 weeks, described as "50 foot walking time (in minutes)" No primary outcome reported
Notes	Two out of 4 groups, the electroacupuncture and ice massage groups, were excluded in this review. *Investigators named their intervention AL-TENS, but we coded it low frequency TENS in our analysis.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	Unclear	Trial protocol not accessible, methods section not explicit about pre-specified outcomes
Adequate blinding of patients?	Yes	Sham device: MEA-TENS with broken lead at jack plug, no current passed but red indicator light on. Quote: "(...) treatment appeared to be done in the same way as the other groups without the subjects suspecting the nature of the stimulation".
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	Investigators reported that "no subject was withdrawn either active or placebo groups". However, the reported degrees of freedom indicate that 5 out of 100 patients were not included. It

Yurtkuran 1999 (*Continued*)

		remained unclear to which of the 4 groups the excluded patients belonged.
Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above
Funding by commercial organisation avoided?	Unclear	No information provided
Funding by non-profit organisation?	Unclear	No information provided

Zizic 1995

Methods	Randomised controlled trial 2-arm parallel group design Trial duration: 34 weeks Multicentre trial with 5 centres No power calculation reported
Participants	78 patients randomised 71 patients with knee OA reported at baseline Study joints: 71 knees Number of females: 33 of 71 (46%)
Interventions	Experimental intervention: pulsed electrostimulation stimulation, daily application Control intervention: sham pulsed electrostimulation, daily application Duration of treatment period: 4 weeks Analgesics allowed, intake assessed and found to be similar between groups. Device: Bionicare Stimulator BIO-1000 Self-administered: yes Waveform: monophasic, spiked Pulse width: unclear Pulse frequency: 100 Hz Amplitude: below sensory threshold, initial increase of amplitude until a tingling sensation was felt then reduction of the amplitude until this sensation disappeared Duration of stimulation: 6 to 10 hours per day Electrodes: 2, unclear whether positioned in knee garment Placement: one on knee, other on thigh directly above that knee
Outcomes	Extracted pain outcome: global pain after 34 weeks described as "Patient evaluation of pain of treated knee (Baseline based on 0-10 VAS, follow-up based on % change from baseline)"

Zizic 1995 (*Continued*)

	Extracted function outcome: patient's global assessment after 34 weeks, described as "Patient evaluation of function of treated knee (Baseline based on 0-10 VAS, follow-up based on % change from baseline)" More than 2 primary outcomes reported (1 physician global evaluation; 2) VAS pain; 3) VAS function)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	No information provided
Free of selective reporting?	No	No results reported for some outcomes mentioned in the methods, including walking time, tenderness and swelling
Adequate blinding of patients?	Yes	Sham device: BIO-1000, identical in appearance to active device, with automatic shut-off as soon as amplitude is reduced (all patients were instructed to reduce intensity just below perception level)
Incomplete outcome reporting: intention-to-treat analysis performed? Pain	No	38 out of 41 (0.93) randomised to experimental and 33 out of 37 (0.89) randomised to control group were analysed
Incomplete outcome reporting: intention-to-treat analysis performed? Function	No	See above
Funding by commercial organisation avoided?	No	Sponsor: Murray Electronics
Funding by non-profit organisation?	Unclear	No information provided

BMI = body mass index
min = minutes
OA = osteoarthritis
VAS = visual analogue scale

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

Barr 2004	Less than 50% of patients diagnosed with osteoarthritis of the knee
Bernau 1981	Not a randomised controlled trial, use of active control groups. Additional description: comparing diadynamic electrostimulation df, diadynamic electrostimulation cf and galvanic current
Burch 2008	Use of active control group. Additional description: randomised controlled trial comparing interferential current stimulation followed by patterned muscle stimulation and low-current transcutaneous electrical nerve stimulation (TENS).
Cauthen 1975	Not concerning osteoarthritis
Commandre 1977	No randomised controlled trial (review)
Cottingham 1985a	Not transcutaneous but subcutaneous application
Cottingham 1985b	Not transcutaneous but subcutaneous application. Abstract referring to same RCT as described in Cottingham 1985a.
Durmus 2005	Use of active control group (exercise)
Gaines 2001	Neuromuscular electrostimulation primarily aiming at muscle strengthening
Gaines 2004	Neuromuscular electrostimulation primarily aiming at muscle strengthening
Gibson 1989	Most likely not a randomised controlled trial; percutaneous electrostimulation primarily aiming at muscle strengthening
Godfrey 1979	Faradic electrostimulation with parameters set to increase muscle strength and use of active control (exercise plus low intensity (sham) faradic electrostimulation)
Grigor'eva 1992	No relevant pain or function outcomes
Guven 2003	High voltage galvanic electrostimulation for muscle strengthening
Hamilton 1959	Only 34% of patients suffered OA; use of active controls. Additional description: cross-over design evaluating faradic electrostimulation.
Huang 2000	TENS as part of a combined experimental intervention. Additional description design: 3 groups, Group A receiving auricular acupuncture, diet control and aerobic exercise, Group B like A with addition of TENS and ultrasound, Group C receiving TENS and ultrasound; unclear whether allocation was at random.
Jensen 1991	Use of active control: high frequency TENS versus low frequency TENS

(*Continued*)

Kang 2007	Percutaneous electrostimulation
Katsnelson 2004	Electrode placement not involving knee innervation: transcranial electrostimulation
Komarova 1998	Electrode placement not involving knee innervation: transcranial electrostimulation
Lewis 1984	Cross-over RCT reporting pooled results after completion of all phases. Contact established with Daniel and Beverly Lewis, who were unable to provide results for the first phase (before cross-over)
Lewis 1985	RCT reporting P values of effect only. Contact established with Daniel and Beverly Lewis, who could not provide any additional outcome data, nor could they indicate whether the design concerned a cross-over or a parallel RCT
Lewis 1988	Published abstract addressing the same cross-over RCT reported by Lewis 1994
Lewis 1994	Cross-over RCT reporting pooled results after completion of all phases. Contact established with Daniel and Beverly Lewis, who were unable to provide results for the first phase (before cross-over)
Lone 2003	Not a randomised controlled study. Additional description: before-after study design that was incorrectly labelled as randomised study by original authors.
Lund 2005	Not concerning osteoarthritis
Macchione 1995	Not a randomised controlled trial (review)
Matti 1987	Not concerning osteoarthritis, not a randomised clinical trial. Tetanus-like faradisation electrostimulation with exercise after surgical removal of meniscus, primarily aiming at muscle enhancement. Active control with 10 Hz sinusoidal current application and exercise.
Miranda-Filloy 2005	Electrical muscle stimulation using sport400 (Complex), primarily aiming at muscle strengthening
Mont 2006	Not a randomised clinical trial. Description: comparative study with historical control evaluating pulsed electrostimulation.
Oldham 1995	Neuromuscular electrostimulation primarily aiming at muscle strengthening
Oldham 1997	Electrostimulation primarily aiming at muscle strengthening
Oosterhof 2008	Mixed population, only 4 out of 163 patients reported to have knee, hip or ankle OA
Paillard 2005	Not concerning osteoarthritis (healthy volunteers)
Picaza 1975	Not concerning osteoarthritis and not a randomised controlled trial

(*Continued*)

Salaj 2001	Not a randomised controlled trial, combined multiple interventions in both interventions and control group
Salim 1996	Not a randomised controlled trial (review)
Sluka 1998	Animal study
Sok 2007	Concerns chronic knee pain. First author was contacted by email to verify how many patients had osteoarthritis. No response received. Additional description: article in Korean, using a TENS device, abstract however suggests that parameters were set to strengthen muscles.
Svarcova 1988a	Use of active control groups. Additional description: controlled trial with groups receiving either galvanic electrostimulation or YES ultrasound or pulsed shortwaves. Within these groups, half of the patients received ibuprofen, half received placebo ibuprofen. It was unclear whether allocation was at random.
Svarcova 1988b	See Svarcova 1988a. Double publication of the same study, including the same number of patient and outcome data.
Svarcova 1990	Use of active control group. Additional description: galvanic electrostimulation versus electroacupuncture.
Talbot 2003	Neuromuscular electrostimulation primarily aiming at muscle strengthening
Tam 2004	No relevant pain or function outcomes used
Taylor 1981	Incomplete presentation of data. Additional description: cross-over randomised clinical trial presenting pooled results only. Contact established with Mark Hallett, who was unable to provide data concerning the first phase, before cross-over. We were unable to contact the other authors.
Tulgar 1991	Not concerning osteoarthritis
Volklein 1990	Use of active control group. Additional description: random allocation of patients to 4 different types of diadynamic current.
Weiner 2007	Not transcutaneous but periosteal (needle) application
Zivkovic 2005	Use of active control group. Additional description: the combination of low-energy laser, pulsed electromagnetic field and kinesitherapy was compared to the combination of electrotherapy, pulsed electromagnetic field and kinesitherapy.

OA = osteoarthritis
RCT = randomised controlled trial
TENS = transcutaneous electrical nerve stimulation

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

Fary 2008

Trial name or title	ACTRNI2607000492459
Methods	Double-blind, randomised placebo-controlled trial Randomisation method: computer-generated block randomisation with stratification for gender, age and intensity of pain Concealment of allocation: by independent administrator Blinding: patients, those administering treatment/s, those assessing outcomes, those analysing results/data Sample size calculation: reported Analyses based on intention-to-treat principle Trial duration: 26 weeks Sponsored by: non-profit organisation Arthritis Australia and Physiotherapy Research Foundation
Participants	70 patients with primary knee OA to be randomised Study joints: 70 knees Selection criteria: persistent, stable pain for minimum of 3 months, at least 25 mm on a 100 mm VAS
Interventions	Experimental intervention: pulsed electrostimulation, daily Control intervention: sham pulsed electrostimulation, daily Duration of treatment period: 26 weeks Analgesics allowed and measured with diary Device: Metron Digi-10s, adapted by engineer Self-administered: yes Waveform: pulsed, exponentially declining Pulse width: not reported Pulse frequency: 100 Hz Amplitude: below sensory threshold Duration of stimulation: minimally 7 hours per day Electrodes: not reported Electrode placement: not reported Sham device: identical in appearance
Outcomes	Primary outcomes: conflicting information reported in Australian/New Zealand clinical trial register (ANZCTR) and subsequent publication in BMC. In ANZCR reported as pain on VAS, in BMC more than 2 primary outcomes are reported; pain (VAS and WOMAC), function (WOMAC), and patient global assessment (VAS). Main time points of interest are reported consistently as baseline, 4, 16 and 26 weeks. Secondary outcomes: in ANZCTR reported as function (WOMAC) and patient global assessment (VAS); in BMC reported as stiffness (WOMAC 3.1), quality of life (SF-36), global perceived effect scale (GPES), physical activity (Human Activity Profile (HAP) questionnaire plus accelerometers Safety outcomes: in BMC, the recording of adverse events was reported
Starting date	26th of September 2007

Fary 2008 (*Continued*)

Contact information	Robyn E Fary Curtin University of Technology, School of Physiotherapy, Kent Street, Bentley, WA, 6102, Australia Tel: 08 9266 3667 Email: R.Fary@curtin.edu.au
Notes	Status at 17 July 2009: open to recruitment

Palmer 2007

Trial name or title	ISRCTN12912789
Methods	A randomised, sham-controlled trial with 3 parallel arms Randomisation method: not reported Concealment of allocation: not reported Blinding: not reported Sample size calculation: not reported Analyses: not reported whether is based on intention-to-treat principle Trial duration: 6 weeks Sponsored by: not reported
Participants	261 (87 in each arm) patients with primary knee OA to be randomised Study joints: knees Selection criteria: knee pain, radiographic (X-ray) evidence of osteophytes, and at least 1 of the following 3 criteria: 50 years or older, morning stiffness that lasts for less than 30 minutes, crepitus on active movement
Interventions	Experimental intervention: TENS, as much as needed and group education including self-efficacy and exercise training, once per week Control intervention 1: Sham TENS, as much as needed and group education once per week, as described above Control intervention 2: group education once per week, as described above Duration of treatment period: 6 weeks Analgesics: unclear wether analgesic intake is allowed and is measured Device: not reported Self-administered: yes Waveform: not reported Pulse width: not reported Pulse frequency: not reported Amplitude: “strong but comfortable” tingling sensation Duration of stimulation: defined as “as much as needed” Electrodes: not reported Electrode placement: within or close to the site of pain Sham device: identical in appearance, displays are active but there is no current output

Palmer 2007 (*Continued*)

Outcomes	Primary outcome: WOMAC function subscale (at baseline, 3, 6, 12 and 24 weeks) Secondary outcomes: 1. Total WOMAC score and WOMAC pain and stiffness subscale scores (at baseline, 3, 6, 12 and 24 weeks) 2. Knee extensor torque (quadriceps strength) (at baseline, 3, 6, 12 and 24 weeks) 3. Patient global assessment of change (at 3, 6, 12 and 24 weeks) 4. Self-efficacy for exercise (at baseline and 24 weeks) 5. Self-reported exercise adherence (at baseline, 3, 6, 12 and 24 weeks) 6. Logged TENS usage time (at 6 weeks)
Starting date	1 October 2007
Contact information	Dr Shea Palmer Faculty of Health and Social Care University of the West of England Blackberry Hill Bristol BS16 1DD United Kingdom Tel +44 (0)117 328 8919 Email Shea.Palmer@uwe.ac.uk
Notes	Status at 17 July 2009: completed at 30 June 2009

OA = osteoarthritis
TENS = transcutaneous electrical nerve stimulation
VAS = visual analogue scale

DATA AND ANALYSES

Comparison 1. Any type of transcutaneous electrostimulation versus control

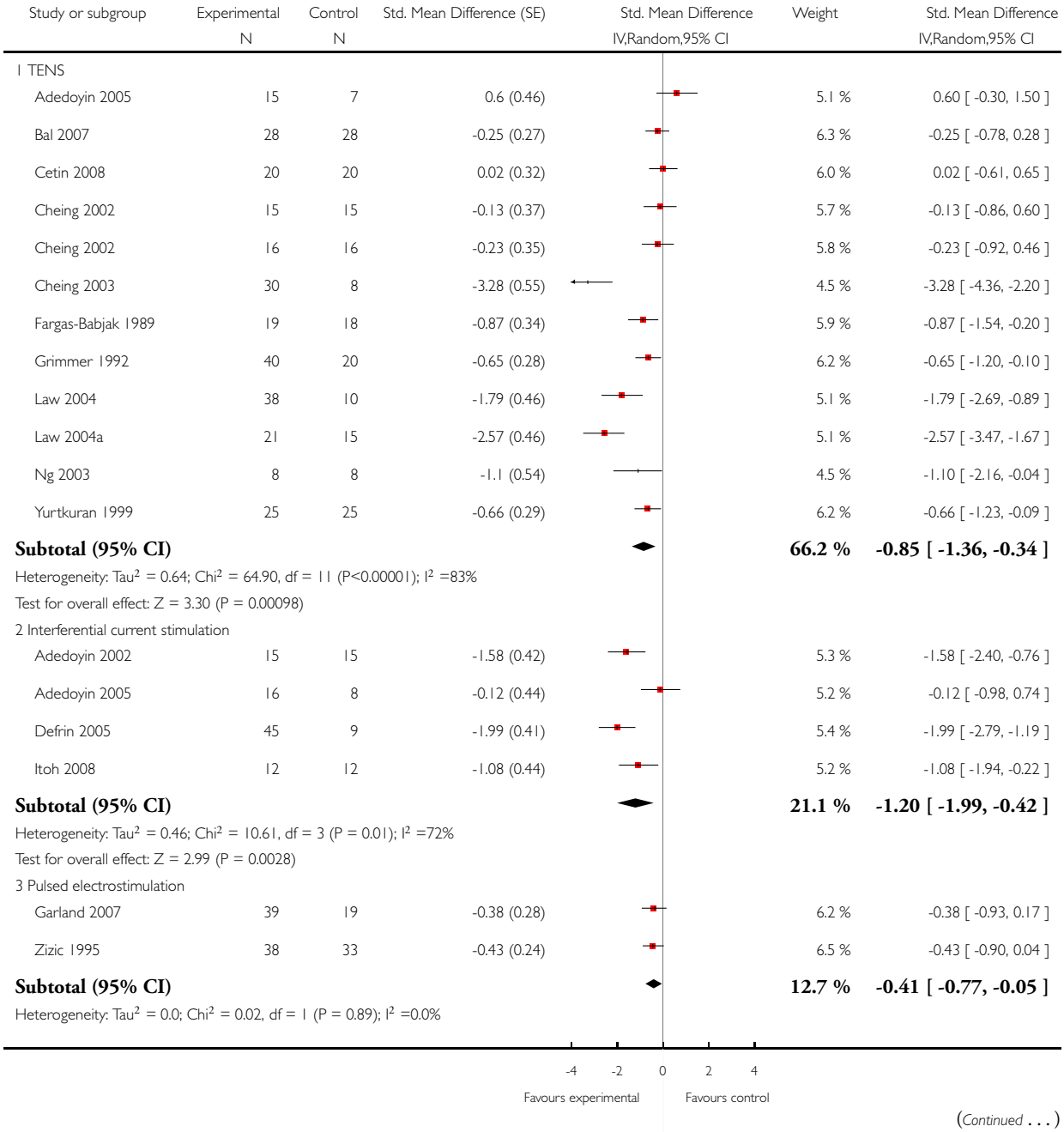
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	16	726	Std. Mean Difference (Random, 95% CI)	-0.86 [-1.23, -0.49]
1.1 TENS	11	465	Std. Mean Difference (Random, 95% CI)	-0.85 [-1.36, -0.34]
1.2 Interferential current stimulation	4	132	Std. Mean Difference (Random, 95% CI)	-1.20 [-1.99, -0.42]
1.3 Pulsed electrostimulation	2	129	Std. Mean Difference (Random, 95% CI)	-0.41 [-0.77, -0.05]
2 Number of patients withdrawn or dropped out because of adverse events	8	363	Risk Ratio (IV, Random, 95% CI)	0.97 [0.16, 6.00]
2.1 TENS	6	255	Risk Ratio (IV, Random, 95% CI)	0.60 [0.03, 14.15]
2.2 Interferential current stimulation	1	30	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.3 Pulsed electrostimulation	1	78	Risk Ratio (IV, Random, 95% CI)	1.80 [0.17, 19.10]
3 Function	9	407	Std. Mean Difference (Random, 95% CI)	-0.34 [-0.54, -0.14]
3.1 TENS	5	204	Std. Mean Difference (Random, 95% CI)	-0.33 [-0.69, 0.03]
3.2 Interferential current stimulation	3	74	Std. Mean Difference (Random, 95% CI)	-0.27 [-0.75, 0.20]
3.3 Pulsed electrostimulation	2	129	Std. Mean Difference (Random, 95% CI)	-0.36 [-0.72, -0.00]
4 Number of patients experiencing any adverse event	3	175	Risk Ratio (IV, Random, 95% CI)	1.02 [0.53, 1.97]
4.1 TENS	1	39	Risk Ratio (IV, Random, 95% CI)	Not estimable
4.2 Pulsed electrostimulation	2	136	Risk Ratio (IV, Random, 95% CI)	1.02 [0.53, 1.97]
5 Number of patients experiencing any serious adverse event	4	195	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 7.32]
5.1 TENS	2	59	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 7.32]
5.2 Pulsed electrostimulation	2	136	Risk Ratio (IV, Random, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Any type of transcutaneous electrostimulation versus control, Outcome 1 Pain.

Review: Transcutaneous electrostimulation for osteoarthritis of the knee

Comparison: 1 Any type of transcutaneous electrostimulation versus control

Outcome: 1 Pain



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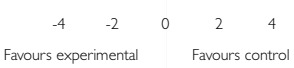
Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Test for overall effect: Z = 2.24 (P = 0.025)						
Total (95% CI)					**100.0 %**	**-0.86 [-1.23, -0.49]**
Heterogeneity: Tau² = 0.50; Chi² = 84.34, df = 17 (P<0.00001); I² =80%						
Test for overall effect: Z = 4.54 (P < 0.00001)						



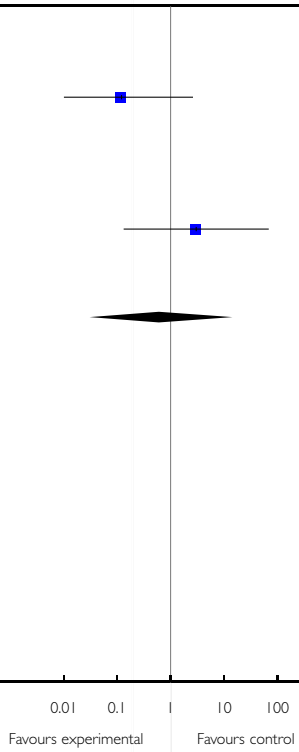
Analysis 1.2. Comparison 1 Any type of transcutaneous electrostimulation versus control, Outcome 2 Number of patients withdrawn or dropped out because of adverse events.

Review: Transcutaneous electrostimulation for osteoarthritis of the knee

Comparison: 1 Any type of transcutaneous electrostimulation versus control

Outcome: 2 Number of patients withdrawn or dropped out because of adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 TENS				
Cheing 2002	0/16	0/18		0.0 [0.0, 0.0]
Cheing 2003	0/30	1/10		0.12 [0.01, 2.69]
Grimmer 1992	0/40	0/20		0.0 [0.0, 0.0]
Law 2004a	0/22	0/17		0.0 [0.0, 0.0]
Smith 1983	1/16	0/16		3.00 [0.13, 68.57]
Yurtkuran 1999	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**149**	**106**		**0.60 [0.03, 14.15]**
Total events: 1 (Experimental), 1 (Control)				
Heterogeneity: Tau² = 2.68; Chi² = 2.05, df = 1 (P = 0.15); I² =51%				
Test for overall effect: Z = 0.32 (P = 0.75)				
2 Interferential current stimulation				
Adedoyin 2002	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**15**	**15**		**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Pulsed electrostimulation				



(*Continued* . . .)

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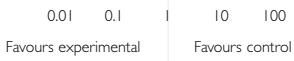
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Zizic 1995	2/41	1/37		1.80 [0.17, 19.10]
Subtotal (95% CI)	**41**	**37**		**1.80 [0.17, 19.10]**
Total events: 2 (Experimental), 1 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.49 (P = 0.62)				
Total (95% CI)	**205**	**158**		**0.97 [0.16, 6.00]**
Total events: 3 (Experimental), 2 (Control)				
Heterogeneity: Tau^2 = 0.54; Chi^2 = 2.51, df = 2 (P = 0.29); I^2 =20%				
Test for overall effect: Z = 0.04 (P = 0.97)				



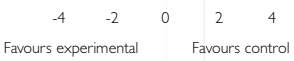
Analysis 1.3. Comparison 1 Any type of transcutaneous electrostimulation versus control, Outcome 3 Function.

Review: Transcutaneous electrostimulation for osteoarthritis of the knee

Comparison: 1 Any type of transcutaneous electrostimulation versus control

Outcome: 3 Function

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 TENS						
Adedoyin 2005	15	7	0 (0.45)		5.2 %	0.0 [-0.88, 0.88]
Bal 2007	28	28	-0.43 (0.27)		14.4 %	-0.43 [-0.96, 0.10]
Cetin 2008	20	20	0.15 (0.32)		10.2 %	0.15 [-0.48, 0.78]
Law 2004a	21	15	-0.28 (0.34)		9.1 %	-0.28 [-0.95, 0.39]
Yurtkuran 1999	25	25	-0.88 (0.3)		11.6 %	-0.88 [-1.47, -0.29]
Subtotal (95% CI)					**50.5 %**	**-0.33 [-0.69, 0.03]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 6.30, df = 4 (P = 0.18); I^2 =36%						
Test for overall effect: Z = 1.78 (P = 0.075)						
2 Interferential current stimulation						
Adedoyin 2005	16	8	-0.36 (0.45)		5.2 %	-0.36 [-1.24, 0.52]
Itoh 2008	12	12	-0.56 (0.42)		5.9 %	-0.56 [-1.38, 0.26]
Quirk 1985	12	14	0.04 (0.39)		6.9 %	0.04 [-0.72, 0.80]



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Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Subtotal (95% CI)					**18.0 %**	**-0.27 [-0.75, 0.20]**
Heterogeneity: Tau² = 0.0; Chi² = 1.15, df = 2 (P = 0.56); I² =0.0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
3 Pulsed electrostimulation						
Garland 2007	39	19	-0.29 (0.28)		13.4 %	-0.29 [-0.84, 0.26]
Zizic 1995	38	33	-0.41 (0.24)		18.2 %	-0.41 [-0.88, 0.06]
Subtotal (95% CI)					**31.5 %**	**-0.36 [-0.72, 0.00]**
Heterogeneity: Tau² = 0.0; Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%						
Test for overall effect: Z = 1.97 (P = 0.049)						
Total (95% CI)					**100.0 %**	**-0.34 [-0.54, -0.14]**
Heterogeneity: Tau² = 0.0; Chi² = 7.64, df = 9 (P = 0.57); I² =0.0%						
Test for overall effect: Z = 3.29 (P = 0.0010)						

-4 -2 0 2 4

Favours experimental Favours control

Analysis 1.4. Comparison 1 Any type of transcutaneous electrostimulation versus control, Outcome 4 Number of patients experiencing any adverse event.

Review: Transcutaneous electrostimulation for osteoarthritis of the knee

Comparison: 1 Any type of transcutaneous electrostimulation versus control

Outcome: 4 Number of patients experiencing any adverse event

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 TENS				
Law 2004a	0/22	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**22**	**17**		**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Pulsed electrostimulation				
Garland 2007	7/39	4/19		0.85 [0.28, 2.56]
Zizic 1995	10/41	8/37		1.13 [0.50, 2.55]
Subtotal (95% CI)	**80**	**56**		**1.02 [0.53, 1.97]**
Total events: 17 (Experimental), 12 (Control)				

0.01 0.1 1 10 100

Favours experimental Favours control

(*Continued* . . .)

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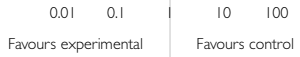
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 1 (P = 0.69); I² =0.0%				
Test for overall effect: Z = 0.06 (P = 0.95)				
Total (95% CI)	**102**	**73**		**1.02 [0.53, 1.97]**
Total events: 17 (Experimental), 12 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 0.16, df = 1 (P = 0.69); I² =0.0%				
Test for overall effect: Z = 0.06 (P = 0.95)				



Analysis 1.5. Comparison 1 Any type of transcutaneous electrostimulation versus control, Outcome 5 Number of patients experiencing any serious adverse event.

Review: Transcutaneous electrostimulation for osteoarthritis of the knee

Comparison: 1 Any type of transcutaneous electrostimulation versus control

Outcome: 5 Number of patients experiencing any serious adverse event

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 TENS				
Cheing 2003	0/10	1/10		0.33 [0.02, 7.32]
Law 2004a	0/22	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**27**		**0.33 [0.02, 7.32]**
Total events: 0 (Experimental), 1 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.70 (P = 0.49)				
2 Pulsed electrostimulation				
Garland 2007	0/41	0/37		0.0 [0.0, 0.0]
Zizic 1995	0/39	0/19		0.0 [0.0, 0.0]
Subtotal (95% CI)	**80**	**56**		**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**112**	**83**		**0.33 [0.02, 7.32]**
Total events: 0 (Experimental), 1 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.70 (P = 0.49)				

APPENDICES

Appendix 1. MEDLINE, EMBASE and CINAHL search strategy

OVID MEDLINE	OVID EMBASE	CINAHL through EBSCOhost
search terms for design 1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trial.sh. 4. random allocation.sh. 5. double blind method.sh. 6. single blind method.sh. 7. clinical trial.pt. 8. exp clinical trial/ 9. (clin$ adj25 trial$).ti,ab. 10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 11. placebos.sh. 12. placebo$.ti,ab. 13. random$.ti,ab. 14. research design.sh. 15. comparative study.sh. 16. exp evaluation studies/ 17. follow up studies.sh. 18. prospective studies.sh. 19. (control$ or prospectiv$ or volunteer$).ti,ab.	*search terms for design* 1. randomized controlled trial.sh. 2. randomization.sh. 3. double blind procedure.sh. 4. single blind procedure.sh. 5. exp clinical trials/ 6. (clin$ adj25 trial$).ti,ab. 7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 8. placebo.sh. 9. placebo$.ti,ab. 10. random$.ti,ab. 11. methodology.sh. 12. comparative study.sh. 13. exp evaluation studies/ 14. follow up.sh. 15. prospective study.sh. 16. (control$ or prospectiv$ or volunteer$).ti,ab.	*Search terms for design* 1. (MH "Clinical Trials+") 2. (MH "Random Assignment") 3. (MH "Double-Blind Studies") or (MH "Single-Blind Studies") 4. TX (clin$ n25 trial$) 5. TX (sing$ n25 blind$) 6. TX (sing$ n25 mask$) 7. TX (doubl$ n25 blind$) 8. TX (doubl$ n25 mask$) 9. TX (trebl$ n25 blind$) 10. TX (trebl$ n25 mask$) 11. TX (tripl$ n25 blind$) 12. TX (tripl$ n25 mask$) 13. (MH "Placebos") 14. TX placebo$ 15. TX random$ 16. (MH "Study Design+") 17. (MH "Comparative Studies") 18. (MH "Evaluation Research") 19. (MH "Prospective Studies+") 20. TX (control$ or prospectiv$ or volunteer$) 21. S1 or S2 or (…….) or S20
Search terms for Osteoarthritis 20. osteoarthriti$.ti,ab,sh. 21. osteoarthro$.ti,ab,sh. 22. gonarthriti$.ti,ab,sh. 23. gonarthro$.ti,ab,sh. 24. coxarthriti$.ti,ab,sh. 25. coxarthro$.ti,ab,sh. 26. arthros$.ti,ab. 27. arthrot$.ti,ab. 28. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab. 29. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	*Search terms for Osteoarthritis* 17. osteoarthriti$.ti,ab,sh. 18. osteoarthro$.ti,ab,sh. 19. gonarthriti$.ti,ab,sh. 20. gonarthro$.ti,ab,sh. 21. coxarthriti$.ti,ab,sh. 22. coxarthro$.ti,ab,sh. 23. arthros$.ti,ab. 24. arthrot$.ti,ab. 25. ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab. 26. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	*Search terms for Osteoarthritis* 22. osteoarthriti$ 23. (MH "Osteoarthritis") 24. TX osteoarthro$ 25. TX gonarthriti$ 26. TX gonarthro$ 27. TX coxarthriti$ 28. TX coxarthro$ 29. TX arthros$ 30. TX arthrot$ 31. TX knee$ n3 pain$ 32. TX hip$ n3 pain$ 33. TX joint$ n3 pain$ 34. TX knee$ n3 ach$ 35. TX hip$ n3 ach$

(*Continued*)

		36. TX joint$ n3 ach$ 37. TX knee$ n3 discomfort$ 38. TX hip$ n3 discomfort$ 39. TX joint$ n3 discomfort$ 40. TX knee$ n3 stiff$ 41. TX hip$ n3 stiff$ 42. TX joint$ n3 stiff$ 43. S22 or S23 or S24….or S42
Search terms for TENS 30. exp electric stimulation therapy/ 31. (electric$ adj (nerve or therapy)).tw. 32. (electric$ adj (stimulation or muscle)).tw. 33. electrostimulation.tw. 34. electroanalgesia.tw. 35. (tens or altens).tw. 36. electroacupuncture.tw. 37. neuromusc$ electric$.tw. 38. high volt.tw. 39. pulsed.tw. 40. (electric$ adj25 current).tw. 41. (electromagnetic or electrotherap$).tw. 42. iontophoresis.tw. 43. transcutaneous nerve stimulation.tw.	*Search terms for TENS* 27. exp electric stimulation therapy/ 28. (electric$ adj (nerve or therapy).tw. 29. (electric$ adj (stimulation or muscle)).tw. 30. electrostimulation.tw. 31. electroanalgesia.tw. 32. (tens or altens).tw. 33. electroacupuncture.tw. 34. neuromusc$ electric$.tw. 35. high volt.tw. 36. pulsed.tw. 37. electric current.sh. 38. (electric$ adj25 current).tw 39. (electromagnetic or electrotherap$).tw. 40. iontophoresis.tw. 41. transcutaneous nerve stimulation.tw.	*Search terms for TENS* 44. (MH "Electric Stimulation+") 45. TX (electric$ n1 nerve) 46. TX (electric$ n1 therapy) 47. TX (electric$ n1 stimulation) 48. TX (electric$ n1 muscle) 49. TX electrostimulation 50. TX electroanalgesia 51. TX tens 52. TX altens 53. TX electroacupuncture 54. TX neuromusc$ electric$ 55. TX high volt 56. TX pulsed 57. TX (electric$ n25 current) 58. TX ((electromagnetic or electrotherap$)) 59. TX iontophoresis 60. TX transcutaneous nerve stimulation 61. S44 or S45 or …. S60
Combining terms 44. or/1-19 45. or/20-29 46. or/30-40 47. and/44-46 48. animal/ 49. animal/ and human/ 50. 48 not 49 51. 47 not 50	*Combining terms* 42. or/1-16 43. or/17-26 44. or/27-37 45. and/42-44 46. animal/ 47. animal/ and human/ 48. 46 not 47 49. 45 not 48	*Combining terms* S21 and S43 and S61

Appendix 2. CENTRAL and PEDro search strategy

CENTRAL	PEDro
Search terms for Osteoarthritis	
#1. (osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro*	1. Electro in title or abstract
OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR	2. Method: clinical trial
((knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*))	3. Body part: thigh or hip
OR ((knee* OR hip* OR joint*) near/3 stiff*)) in Clinical Trials	4. Body part lower leg or knee
#2. MeSH descriptor Osteoarthritis explode all trees	Combination 1. and 2. and 3.
Search terms for TENS	Combination 1. and 2. and 4.
#3. MeSH descriptor Electric Stimulation Therapy explode all trees	1. TENS in title or abstract
#4. electric* near/ (nerve or therapy) in Clinical Trials	2. Method: clinical trial
#5. electric* near/ (stimulation or muscle) in Clinical Trials	3. Body part: thigh or hip
#6. electrostimulation in Clinical Trials	4. Body part lower leg or knee
#7. electroanalgesia in Clinical Trials	Combination 1. and 2. and 3.
#8. tens or altens in Clinical Trials	Combination 1. and 2. and 4.
#9. electroacupuncture in Clinical Trials	Combine all
#10. neuromusc* electric* in Clinical Trials	
#11. high volt in Clinical Trials	
#12. pulsed in Clinical Trials	
#13. (electric* near/25 current) in Clinical Trials	
#14. (electromagnetic or electrotherap*) in Clinical Trials	
#15. iontophoresis in Clinical Trials	
#16. transcutaneous nerve stimulation in Clinical Trials	
Combining terms	
#17. (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR	
#11 OR #12 OR #13 OR #14 OR #15 OR #16)	
#18. (#1 OR #2)	
#19. (#17 AND #18) in Clinical Trials	

WHAT'S NEW

Last assessed as up-to-date: 1 February 2009.

17 July 2009	New citation required and conclusions have changed	Change in authors and conclusions. Updated search and wider selection criteria, which resulted in 14 additional trials; more detailed quality assessment of component trials; exclusion of results from cross-over trials if treatment phases could not be distinguished; use of end of trial estimates to calculate SMDs; detailed exploration of sources of variation between trials, including concealment of allocation, blinding, intention-to-treat analysis, characteristics of electrostimulation, and investigations of funnel plots; use of a random-effects model.
17 July 2009	New search has been performed	14 additional trials included
1 May 2008	Amended	CMSG ID C094-R

HISTORY

Review first published: Issue 4, 2000

30 April 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Study conception: Rutjes, Jüni

Protocol development: Rutjes, Nüesch, Hendriks, Kalichman, Reichenbach, Jüni

Acquisition of data: Rutjes, Nüesch, Sterchi, Kalichman, Hendriks, Osiri, Brosseau, Reichenbach, Jüni

Analysis and interpretation of data: Rutjes, Nüesch, Sterchi, Hendriks, Kalichman, Osiri, Brosseau, Reichenbach, Jüni

Drafting of the manuscript: Rutjes

Critical revision of the manuscript for important intellectual content: Rutjes, Nüesch, Sterchi, Hendriks, Kalichman, Reichenbach, Jüni

Statistical analysis: Nüesch, Jüni, Rutjes

Obtained funding: Reichenbach, Jüni

Dr Rutjes and Mrs Nüesch contributed equally to this article.

DECLARATIONS OF INTEREST

None.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Before embarking on this review, we generated a standard protocol for this and all other Cochrane Reviews performed by our group. The protocol was approved by the Editorial Board of the Cochrane Musculoskeletal Review Group (CMSG), but, as an update, did not result in a specific publication in the Cochrane database. We deviated from the standard protocol with respect to the selection of main outcomes and analysis. The main outcomes specified in the protocol were pain and function, as recommended for osteoarthritis trials. After approval of the standard protocol, the Editorial Board of CMSG reconvened several times to establish common views on how to conduct systematic reviews, and it was decided that the main outcomes of future reviews should reflect both effectiveness *and* safety. CMSG further agreed to recommend the use of a maximum of two main outcomes. Therefore, the CMSG Editorial Board and the authors of this review agreed to specify pain intensity and the number of drop-outs or withdrawals due to adverse events as main outcomes for this update. Function was specified as one of the secondary outcomes. The protocol specified that our main analysis would be based on standardised mean differences (SMDs) derived from inverse-variance random-effects meta-analysis. In view of the high degree of heterogeneity, the predominance of small trials of low methodological quality and the skewed funnel plot for pain intensity as one of the main outcomes, we refrained from presenting the SMD of pain as primary result in main body of text and summary of findings table, but reported results from uni-variable meta-regression analysis used to predict treatment effects in trials as large as the largest trials included in the meta-analysis with the standard error as the explanatory variable. We acknowledge that this analysis is exploratory, however. In addition, we used 'Risk of bias' tables to present the methodological quality of included trials and a 'Summary of findings' table to present results.

INDEX TERMS

Medical Subject Headings (MeSH)

Osteoarthritis, Knee [*therapy]; Outcome Assessment (Health Care); Randomized Controlled Trials as Topic; Transcutaneous Electric Nerve Stimulation [*methods]

MeSH check words

Humans