Transcutaneous electrical nerve stimulation for knee osteoarthritis (Review)

Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P, Wells G

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ABSTRACT

Background
Osteoarthritis (OA) is a disease that affects synovial joints causing degeneration and destruction of hyaline cartilage. To date, no curative treatment for OA exists. The primary goals for OA therapy are to relieve pain, maintain or improve functional status, and minimize deformity. Transcutaneous electrical nerve stimulation (TENS) is a noninvasive modality that is commonly used in physiotherapy to control both acute and chronic pain arising from several conditions. A number of trials evaluating the efficacy of TENS in OA have been published.

Objectives
To assess the effectiveness of TENS in the treatment of knee OA, studies of one year or longer were included in the review. The primary outcomes of interest were those described by the Outcome Measures in Rheumatology Clinical Trials (OMERACT 3), which included pain relief, functional status, patient global assessment and change in joint imaging. The secondary objective was to determine the most effective mode of TENS application for pain control.

Search strategy
We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, CINAHL, HEALTHSTAR, PEDro and Current Contents (to December 1999) using the Cochrane Musculoskeletal Group search strategy . We also hand-searched reference lists and consulted content experts.

Selection criteria
Two independent reviewers selected the trials that met predetermined inclusion criteria.

Data collection and analysis
Two independent reviewers extracted the data using standardized forms and assessed the quality of studies for randomization, blinding and dropouts. A third reviewer was consulted to resolve any differences. For dichotomous outcomes, relative risks (RR) were calculated. For continuous data, weighted mean differences (WMD) or standardized mean differences (SMD) of the change from baseline were calculated. A fixed effects model was used unless heterogeneity of the populations existed. In this case, a random effects model was used.

Main results
Seven trials were eligible to be included in this review. Six used TENS as the active treatment while one study used acupuncture like TENS (AL-TENS). A total of 148 and 146 patients were involved in the active TENS treatment and placebo groups respectively. Three studies were cross-over studies and the other four were parallel group, randomized controlled trials (RCTs). The median methodological quality of these studies was three out of five. Pain relief from active TENS and AL-TENS treatment was significantly better than placebo treatment. Knee stiffness also improved significantly in the active treatment group compared to placebo. Different modes of TENS settings (high frequency and strong burst mode TENS) all demonstrated a significant benefit in pain relief of the knee OA over placebo. Subgroup analyses showed a heterogeneity in the studies with methodological quality of three or more and those with repeated TENS applications.

Authors' conclusions
TENS and AL-TENS are shown to be effective in pain control over placebo in this review. Heterogeneity of the included studies was observed, which might be due to the different study designs and outcomes used. More well designed studies with a standardized protocol and adequate numbers of participants are needed to conclude the effectiveness of TENS in the treatment of OA of the knee.

PLAIN LANGUAGE SUMMARY

TENS and AL-TENS over at least four weeks are effective for pain control and relief of knee stiffness in osteoarthritis

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive modality with very few adverse effects that is used in physiotherapy for control of pain. Seven studies using TENS in people with knee osteoarthritis (OA) were identified for this review; device setting, application and outcomes measured varied between studies. Active TENS and 'acupuncture like' TENS (AL-TENS) treatment for at least four weeks effectively reduced pain. Knee stiffness also improved significantly. More well designed studies, with a large study population and sufficient intervention period, are needed to determine the overall effectiveness of TENS for the treatment of knee OA.

BACKGROUND

Osteoarthritis (OA) is primarily a disease of cartilage as it is characterized by the degradation of hyaline cartilage in the joints (Solomon 1997). It is believed to be a dynamic disease that reflects the balance between destruction and repair (Solomon 1997). The destruction processes of cartilage: softening and fibrillation, exposure of the subarticular bone plate, and fragmentation of the subchondral trabeculae, are accompanied by hyperactive new bone formation, osteophytosis, and bone remodeling (Solomon 1997). OA is the most common form of arthritis and one of the most important causes of long-term disability in adults (Solomon 1997, Peyron 1992). OA has a worldwide distribution though there is a variation in the prevalence among different ethnic groups and genders. However, OA mainly affects the elderly population. The prevalence of OA in populations older than 60 years of age is more than 50% (Solomon 1997). The common sites of joints to develop OA include the knee, hand, hip, spine and foot. Of these, OA of the knee is most commonly found. In addition to increasing age, OA of the knee is associated with obesity, trauma, history of inflammatory arthritis and certain metabolic diseases such as acromegaly and calcium pyrophosphate dihydrate (CPPD) arthropathy (Fife 1997). Common complaints in people with knee OA are pain exacerbated by movement or weight bearing, stiffness, swelling and deformity (genu varum or genu valgum), and restricted walking distance.

The objectives of management of OA of the knee are to relieve pain, maintain or improve mobility, and minimize disability. Treatment options include non-pharmacologic intervention, drug therapy, and surgery (Fife 1997). Different modalities in physiotherapy have been shown to help improve clinical symptoms and function of knee OA, with fewer adverse effects than medical treatment. Transcutaneous electrical nerve stimulation (TENS) is among these non-invasive therapies.

TENS therapy has been used to treat a variety of painful acute and chronic conditions (Puett 1994, Gersh 1985, Lampe 1978). This neuromodulatory method is based on the 'Gate-Control Theory' of pain perception as described by Melzack and Wall (Melzack 1965). Pain impulses are transmitted to the spinal cord via small cutaneous (delta) fibers. TENS stimulates large cutaneous (beta) fibers that subsequently transmit a faster impulse via C-fibers to inhibit the pain signals from the small fibers. Thus, TENS devices were designed to be used as afferent nerve stimulators that provide adequate pain relief without involving invasive procedures. Several studies have shown that TENS may also stimulate endogenous opiates secretion (Andersson 1976, Grimmer 1992, Mayer 1989). Three important factors that determine the quality of a TENS device include: (1) selection of functioning mode (e.g. stimulators, electrode type, design); (2) the wave form of the device, which is modified by adjusting the amplitude, rate, and width controls; and (3) the proper location of electrodes (Lampe 1978).

Four types of TENS device settings are currently used in clinical practice: 1) high frequency (40 to 150 Hz, 50 to 100 μsec pulse width, moderate intensity); 2) low frequency (1 to 4 Hz, 100 to 400 μsec pulse width, high intensity); 3) burst frequency (1 to 4Hz with high internal frequency, 100 to 250 μsec pulse width, high intensity); and 4) hyperstimulation (1 to 4Hz, 10 to 500 msec pulse width, high intensity) (Jette 1986).

OBJECTIVES

To determine the efficacy of transcutaneous electrical nerve stimulation (TENS) in the treatment of osteoarthritis (OA) of the knee.

A secondary purpose was to determine the most effective mode of TENS application for knee OA, including the optimal characteristics of the following:
- Mode of function (types of stimulator, electrode and design);

- Pulse form (intensity, rate and width);
- Electrode placement site;
- Frequency and duration of treatment.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that were eligible according to an a priori protocol.

Types of participants

Only trials with people, aged 18 years or more, with clinical and/or radiological confirmation of OA of the knee were included. Diagnosis of knee OA was defined using the American College of Rheumatology (ACR) criteria of classification of OA of the knee (Altman 1986). No participants had any surgical intervention of the affected knee.

Types of intervention

All types of TENS were included in this review. Trials that compared TENS intervention with standard treatment and/or placebo were included.

Types of outcome measures

The primary outcome measure was pain relief, according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT 3) (Bellamy 1997). In addition, the other outcome measures from OMERACT 3 were also included for potential analysis.

OMERACT measures for OA include:
- Pain;
- Physical function;
- Patient global assessment;
- Joint imaging (for studies of one year or longer).

In addition, the outcome measures recommended by Morin and colleagues (Morin 1996) were included. They were:
- Duration of morning stiffness;
- Quadriceps muscle strength;
- Knee range of motion (ROM);
- Knee circumference;
- Walking distance and walking time.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Published clinical trials of TENS for knee OA were identified through a search of the Cochrane Musculoskeletal Group register, Cochrane Controlled Trial Register (CCTR) issue 1, 2000, MEDLINE (1966 to 1999), EMBASE (1975 to 1999), CINAHL, HEALTHSTAR and Physiotherapy Evidence Database (PEDro) using the sensitive search strategy of the Cochrane Musculoskeletal Group based on work by Dickersin 1994 and Haynes 1994.

Reference lists were handsearched for further identification of published work, presentations at scientific meetings and personal communications. Content experts were contacted for additional studies and unpublished data (Dickersin 1997).

The search strategy used for the MEDLINE database is as follows:

1. pain.tw,hw.
2. activities of daily living/
3. (joint$ adj4 (mobility or flexibility)).tw.
4. (return$ adj3 (work or leisure)).tw.
5. (function$ adj2 (status or abilit$)).tw.
6. (stiffness or swelling or swollen or tender).tw.
7. (flexion or extension or abduction or adduction).tw.
8. range of motion, articular/
9. (range adj2 motion).tw.
10. (strength or power).tw.
11. (grip$ or force or rotation).tw.
12. (dynamomet$ or goniomet$).tw.
13. absenteeism/ or absenteeism.tw.
14. (sick leave or sick day$ or absence).tw.
15. sick leave/
16. (disabilit$ or (work$ adj compensation)).tw.
17. cost$.tw.
18. exp economics/ or ec.fs.
19. or/1-18
20. exp electric stimulation therapy/
21. ((electric$ adj nerve) or therapy).tw.
22. ((electric$ adj (stimulation or muscle)).tw.
23. electrostimulation.tw.
24. electroanalgesia.tw.
25. (tens or altens).tw.
26. electroacupuncture.tw.
27. neuromusc$ electric$.tw.
28. (high volt or pulsed or current).tw.
29. (electromagnetic or electrotherap$).tw.
30. iontophoresis.tw.
31. or/20-30
32. knee.sh,tw.
33. exp knee joint/
34. osteoarthritis/
35. osteoarthr$.tw.
36. (32 or 33) and (34 or 35)
37. 31 and 36
38. animal/ not (human/ and animal/)
39. 37 not 38
40. randomized controlled trial.pt.
41. controlled clinical trials/

42. exp cross-sectional studies/
43. controlled clinical trial.pt.
44. cross-section$.tw.
45. prospective.tw.
46. retrospective.tw.
47. exp cohort studies/
48. exp case-control studies/
49. random$.tw.
50. control$.tw.
51. (compare or comparative).tw.
52. comparative studies/
53. experiment$.tw.
54. or/40-53
56. 39 and 54

METHODS OF THE REVIEW

The above search strategy identified a set of potentially relevant articles. These trials were assessed by two independent reviewers (LB, MO). Studies were selected for inclusion in the review according to the inclusion criteria.

From each included trial, we collected information regarding the trial design, participant characteristics, dosages i.e. modes of TENS application, treatment periods, baseline and end of study outcomes. Data concerning details of the studied population, intervention and outcomes were extracted by two independent reviewers (LB, MO) using pre-determined extraction forms. Differences in data extraction were resolved by referring back to the original article and establishing consensus. A third reviewer (VW) was consulted to help resolve differences. When necessary, information was sought from the authors of the primary studies.

Where possible, the analyses were based on intention-to-treat data from the individual clinical trials. Subgroup analyses were conducted to examine the efficacy of TENS with different application methods and modes (including frequency, length of treatment and techniques). A sensitivity analysis was conducted based on the methodological quality of each trial.

Statistical analysis

All of the data from the individual trials were entered into a spreadsheet. This spreadsheet provided the data for the Review Manager software (RevMan 4.0), which was used for both descriptive and statistical data. For continuous data, results were presented as a weighted mean difference (WMD). However, where different scales were used to measure the same concept or outcome, standardized mean differences (SMD) were used. For dichotomous data, relative risk (RR)s were used (Petitti 1994, Hennekens 1987). Heterogeneity was calculated using a Chi square test and considered significant when the probability (P-value) was less than 0.05. Fixed effects models were used throughout unless heterogeneity was significant, in which case a random effect model was used. Publication bias was not assessed due to the probable small number of studies.

DESCRIPTION OF STUDIES

The search strategies retrieved 210 articles. From these, nine RCTs met the inclusion criteria of which seven studies (294 participants) were included in the meta-analysis. The reasons for not including the other two trials were: only descriptive results were given in one trial (Jensen H 91); the device was not considered to be TENS in the other (Zizic 1995).

The included RCTs involved 148 participants in the active TENS treatment and 146 participants in the placebo groups. Three studies were cross-over studies (Taylor 1981, Lewis D 1984, Lewis B 1994), two were randomized single-blind, parallel group studies (Smith 1983,Yurtkuran 1999) and the other two were double-blind, placebo-controlled trials (Fargas-Babjak 1989, Grimmer 1992). Four studies used high frequency mode TENS while the trial by Fargas-Babjak and colleagues (Fargas-Babjak 1989) used strong burst mode TENS. The study by Grimmer 1992 was a three-arm trial comparing the efficacy of high frequency TENS with that of burst mode TENS and placebo. The study by Yurtkuran and Kocagil (1999) was a four-arm study comparing the efficacy of acupuncture like TENS (AL-TENS) to those of electroacupuncture (EA), ice massage and placebo.

All of the participants in the included trials were diagnosed with knee OA based on clinical and/or radiographic evidences. All had painful knee OA that required pharmaceutical intervention. Although the studied population in the included RCTs seemed to be homogeneous, the TENS application protocols were markedly diverse. Differences included the modes of stimulation, optimal stimulation levels, pulse frequencies, electrode placements, lengths of stimulation time and how often TENS was applied. The results of this meta-analysis were stratified by the duration and modes of TENS application. The outcome measures also varied from one study to another.

METHODOLOGICAL QUALITY

The quality of the included studies was assessed using a scale developed by Jadad (Jadad 1996, Clark 1999), which included the appropriateness of randomization and of blinding, and consideration of dropouts and withdrawals in statistical analysis.

Quality was assessed independently by two reviewers (LB, MO). Differences were resolved by consensus. A third reviewer (VW) was consulted if necessary. Studies were divided into low and high quality, based on the median quality score, to examine the effect of quality on outcome measures. The maximum quality score was five. Studies with a score less than three were considered low quality

studies while those with scores of at least three were classified as high quality studies.

Median quality of the included studies was 3. One study scored 1, two scored 2 and four scored 3.

RESULTS

Efficacy of TENS and/or AL-TENS compared to placebo

When the combined efficacies of TENS and AL-TENS were compared to placebo and expressed as standardized mean difference (SMD) with 95% confidence intervals (CI), pain relief, measured using a visual analogue scale (VAS), improved significantly in the treatment group [SMD -0.448 VAS (95%CI: -0.703 to -0.192)]. There were only two individual studies for which the results were significant, i.e. the study by Fargas-Babjak (Fargas-Babjak 1989) and the AL-TENS study by Yurtkuran and Kocagil (Yurtkuran 1999). This analysis used the random effects model, due to the heterogeneity of the included trials.

Stiffness of the knee was also improved significantly in the combined TENS/ AL-TENS treatment group compared to placebo as shown by the weighted mean difference (WMD) [WMD -5.972 cm (95% CI: -9.89 to -2.055)].

If only the studies of TENS application compared to placebo were analyzed, pain measured on a VAS was still significantly less in the TENS group [SMD -0.38 VAS (95%CI: -0.655 to -0.104)]. The analysis of TENS versus placebo studies still showed heterogeneity. The result was similar when AL-TENS was compared to placebo; the WMD of pain relief was -0.8 cm (95% CI: -1.386 to -0.214) in favour of AL-TENS. The other outcomes: stiffness of the knee [WMD -7.9 cm (95% CI -12.099 to -3.701)], 50-foot walking time [WMD -22.6 minutes (95% CI -43.012 to -2.188)], quadriceps muscle strength [WMD -5.2 kg (95% CI -7.853 to -2.547)], and knee flexion [WMD -11.3 degrees (95% CI -17.592 to -5.008)] were also improved significantly in the AL-TENS group compared to placebo.

The number of participants reporting pain improvement was significantly different between the TENS treated group and placebo group [RR 2.41 (95% CI: 1.58 to 3.69)]. The participants in the TENS treatment group were more than twice more likely to have pain improvement than those in the placebo group. After they finished their courses of TENS treatment, the participants in this group still did better than those in the placebo group regarding pain improvement as shown in follow up studies [RR 2.7 (95%CI: 0.94 to 7.72)]. However, heterogeneity existed in this analysis, which may be explained by the result from one study being significant while the other was not.

For the study by Grimmer 1992, we did a separate analysis of two different kinds of TENS applications compared to placebo. After one application, pain relief with high frequency TENS application was significantly better than placebo [WMD -2.1cm (95% CI: -4.115 to -0.085)] while the difference in pain relief between strong burst mode TENS and placebo did not reach a significant level [WMD -1.6 cm (95% CI: -3.209 to 0.009)].

Subgroup Analysis:

Methodological quality
The quality scores of the included trials did not exceed 3. Three studies with the quality scores of 1 and 2 were compared to the other four with a score of 3. Heterogeneity was observed in the results from studies with high quality scores. Using a random effects model, pain relief was significantly different from placebo in high quality studies [SMD -0.582 (95% CI: -0.934 to -0.23)] but not in low quality studies (SMD -0.291 (95%CI: -0.654 to 0.072)].

High frequency TENS versus strong burst mode TENS versus AL-TENS
No heterogeneity was found within each mode of TENS setting. However, pain relief by strong burst mode TENS and AL-TENS was approximately two times better than with high frequency TENS. The pain relief when strong burst mode TENS was compared to placebo was [SMD -0.72 (95% CI: -1.183 to -0.256)], when AL-TENS was compared to placebo was [SMD -0.745 (95% CI: -1.32 to -0.17)], and when high frequency TENS was compared to placebo was [SMD -0.332 (95% CI: -0.648 to -0.016)].

Single versus repeated applications
Heterogeneity was observed in the results from studies with repeated TENS applications. Thus, the random effects model was used. Pain relief was not significant in the study with single TENS application [SMD -0.633 cm (95% CI -1.27 to -0.004)] but improved significantly in studies with repeated TENS applications [SMD -0.324 cm (95% CI -0.645 to -0.003)].

Length of duration of TENS application
The duration of TENS application in each session in the included studies ranged from 20 to 60 minutes and the length of the experimental intervention period varied from one treatment session to six week sessions. The efficacy of TENS for pain relief in studies with intervention period less than four weeks was not significantly different from placebo [SMD -0.288 (95%CI: -0.585 to 0.009)]. On the other hand, TENS application for at least four weeks showed a significant efficacy in pain relief compared to placebo [SMD -0.85 (95% CI: -1.527 to -0.174)].

DISCUSSION

Osteoarthritis (OA) is one of the most important causes of chronic pain in the general population (Peyron 1992, Solomon 1997). [(Solomon 1997, Peyron 1992)] Treatment of pain in patients with OA is mainly with analgesic medications that can cause serious adverse events in long-term use. To avoid the adverse effects from these drugs other modalities have been introduced and

their effectiveness has been demonstrated. TENS is one non-invasive modalities recognised to be helpful in pain control. In addition to OA, TENS has been used to relieve acute and chronic pain caused by various etiologies (Gersh 1985, Lampe 1978, Puett 1994). Studies regarding the use of TENS for pain relief in OA have been conducted but the results are controversial. The objective of this systematic review was to evaluate the efficacy of TENS in the treatment of knee OA.

All of the study participants had OA of one or both knees, diagnosed by clinical symptoms and radiographic evidence, and the OA was painful despite medical treatment. The protocols for TENS device setting and application varied widely between studies, as well as the outcome measures. Study designs included parallel group and cross-over studies. For the cross-over studies, only data from the first intervention was collected in order to eliminate the carry-over effects of earlier interventions. Modes of TENS device settings used in the included trials were conventional (high frequency or strong burst mode) and acupuncture-like TENS. High frequency TENS has been shown to affect the central and peripheral mechanisms of pain control (Melzack 1965, Andersson 1976). Strong burst mode TENS stimulates intrinsic endogenous opiates secretion as well as rhythmic muscle contractions (Lundberg 1984). For AL-TENS, low frequency, high intensity pulses applied to somatic acupuncture points are used (Shealy 1993). AL-TENS has been shown to increase the pain threshold (Yurtkuran 1999).

Pain relief, measured both by using a visual analogue scale (VAS) and the number of participants experiencing pain relief, was significantly different between the TENS and placebo groups. Strong evidence came from the study comparing strong burst mode TENS to placebo, for six weeks, which showed a significant benefit in pain relief from TENS (Fargas-Babjak 1989). This study had a methodological quality score of three and was a double-blind RCT. Thus, the efficacy of TENS from this study was quite acceptable. Other outcomes including ambulation, stiffness, knee circumference and knee range of motion were not significantly different between the treatment and placebo groups. This might be explained by the low methodological quality of the included studies measuring these outcomes, a wide variety of TENS devices used and application protocols, or inadequate intervention periods (short trials). Results from the AL-TENS study, however, showed a promising improvement in all outcomes, at two weeks, compared to placebo. This study was a double-blind RCT with a quality score of three. There has been evidence that the neuroregulatory effects and pain transmission moderation effects of the TENS are more effective with higher intensity application (Langley 1984)), such as with the acupuncture-like application. Moreover, AL-TENS might also act in the same manner as traditional acupuncture.

Interestingly, when two different modes of TENS applications were compared to placebo in the study by Grimmer 1992, high frequency TENS reduced the pain significantly but there was no significant difference in pain relief between strong burst mode TENS and placebo. However, in the subgroup analysis when the results of the other studies were pooled, both high frequency and strong burst mode TENS improved pain significantly, and the strong burst mode TENS improved the pain even more than did high frequency TENS. This might be explained by the effects of the other studies, which outweighed the results of the study by Grimmer.

The median and highest quality score of the included studies was three. Three studies had quality scores less than three. The explanation of these low quality scores could be because of the difficulty to perform appropriate randomization or appropriate double blinding. Insufficient information was noted in several RCTs about the treatment assignment procedure. 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). A valid placebo in TENS RCTs is difficult to find since TENS involves cutaneous stimulation. Not all studies reported adequate information regarding withdrawals and loss to follow up, nor indicated whether they were considered in the data analysis. These weaknesses contribute to the lower quality assessment scores in this systematic review.

Regarding the other outcome measures of knee OA, there was a large variety in the outcomes used in each of the included studies. Most of them could not be pooled. Only stiffness of the knee could be pooled and the pooled estimate was significant in the combined TENS/ AL-TENS group.

Although the included trials were all published articles, the number of trials with nonsignificant results (four) was comparable to those with significant results (three). A funnel plot, to test the impact of publication bias on the results, was not performed since the number of the included trials was not large enough to do so. The participants enrolled were those with a definite diagnosis of OA but heterogeneity in the disease (e.g. stage and severity of knee OA) and the people (e.g. lifestyle, co-morbid diseases and concomitant medication) might exist; detailed information on demographic data was incomplete. Variations in the studied participants might, therefore, affect the study results.

No side effect of the TENS treatment was reported in the included trials. This might be because of the relative safety of the TENS, which could be an advantage over the use of analgesic medication.

Subgroup analyses of different frequencies of TENS application and methodological quality showed heterogeneity, in the results from studies with repeated TENS administration and those with quality scores of three or higher. After an appropriate statistical calculation adjustment, a significant difference in pain relief was observed in the studies with higher methodological quality, both modes of TENS device settings, repeated TENS application, and an intervention period of TENS application of at least four weeks.

AUTHORS' CONCLUSIONS

Implications for practice

Both high frequency and strong burst mode TENS showed a significant benefit on pain relief in the treatment of knee OA. However, when stratified by intervention period, TENS treatment did not show a significant efficacy in pain relief over placebo if the treatment duration was less than four weeks. Only a randomized, double-blind, placebo controlled trial with treatment duration of six weeks has shown that TENS can significantly improve pain relief compared to placebo. A two week study has shown that the AL-TENS is effective in pain relief, decreasing stiffness and walking time, improving quadriceps muscle strength and knee flexion compared with placebo. Subgroup analyses have shown that heterogeneity does exist in the results from studies with different methodological quality scores and different administrations of TENS. TENS may be used as an alternative for pain relief in OA of the knee due to its non-invasive application and few adverse events.

Implications for research

Better study designs are needed to conclude the efficacy of TENS in the treatment of knee OA. The studies should be two-arm, randomized, double-blind, placebo controlled trials with an intervention period long enough to detect a difference (at least six weeks). A regulated study protocol should be developed to standardize the TENS setting, electrode placement and duration of application. The outcome measures should be standardized and contain appropriate subjective and objective outcomes. These will make the studies more reliable and comparable.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Fargas-Babjak 1989
Methods	Randomized, double-blind, controlled trial Sample size at entry: 56 Dropouts: 19 in both groups Treatment duration: 6 weeks Follow up: 3 months
Participants	Patients with painful OA hip and knee for > 6 months No change in their medication Exclude: patients involved in legal litigation, were pregnant, had a pacemaker, on glucocorticoid, change their medication within 3 months, failed to answer the questionnaires in a consistent manner Age: 29-81 years Gender not available Patients completed the study: 37 (19 in treatment group, 18 in placebo group)
Interventions	TENS: schedule: 30 minutes, twice daily for 6 weeks. The first 2 treatments were performed in the clinic by a trained nurse. waveform: square pulses pulse frequency: 4 Hz and the burst frequency at 200 Hz for 125 ms length current: to make a tingling sensation electrode placement: on different 13 areas on the acupuncture and tender points of hip and knee Placebo: same with a frequency of 0.2 Hz with a threshold electrical stimulus of 0.5 mA
Outcomes	At 6 weeks: number of patients with 1) improvement of VAS pain scale > 25% 2) improvement of West Haven Yale Scale of pain > 1.0 unit

Characteristics of included studies (*Continued*)

	3) improvement of functional status, goniometry of knee and hip, knee circumference, 50-foot walking time, and tenderness of joint and soft tissue At 3 months: telephone inquiry of the patient global assessment
Notes	Quality = 3 (R1, D1, W1)
Allocation concealment	B – Unclear

Study	**Grimmer 1992**
Methods	Randomized, double-blind, controlled trial with active and placebo comparators Sample size at entry: 60 (20 in each group) No dropouts reported Treatment duration: once for 30 minutes Follow up: immediate after treatment
Participants	Patients who had knee pain from OA with radiologic diagnosis for => 6 months, withhold all analgesics, muscle relaxants, and NSAIDs => 48 hours before the test, never been on TENS, can complete absolute VAS, on hearing aid or cardiac pacemaker, and physically fit enough. If had bilateral knee pain, would consider only the most painful knee. Male/female: 7/13, 8/12, 8/12 Mean (SD) age: 65.6 (16.2), 65.7 (16.5), 68.4 (11.3) Mean (SD) OA duration: 5.6 (6.6), 9.9 (10.5), 7.9 (9.0)
Interventions	TENS device: MEDTRONIC NEUROMED SELECTRA Electrodes: 4 carbon/rubber/silicone electrodes size 2x3 cm. Electrode placement: 4 acupuncture points around the knee: medial (spleen 9), lateral (gall bladder 33), posterior (urinary bladder 40), anterior (spleen 10) Skin preparation: wash skin around the knee with warm water and soap, rinse with warm water and dry with towels Gel: thin coat of Sealsystems Gel (Page Medical) Treatment time: 30 minutes once Stimulation mode: Group 1: conventional High Rate TENS with current of 80 Hz Group 2: strong Burst Mode TENS with current of 3 Hz trains of seven 80 Hz pulses Placebo: same device with non-functioning electrodes
Outcomes	1) Immediate pain relief (vertical absolute VAS) in cm. 2) Length of pain relief in hours 3) Immediate stiffness measurement (AVAS) in cm. 4) Length of stiffness relief in hours 5) Knee circumference in cm. 6) knee range of motion (using goniometer)
Notes	Quality = 2 (R2, D0, W0)
Allocation concealment	B – Unclear

Study	**Lewis B 1994**
Methods	Randomized, crossover placebo controlled trial Sample size at entry: 36 in all 3 groups

Characteristics of included studies (*Continued*)

	Dropouts: 10 Treatment duration: 9 weeks (3 weeks for each treatment)
Participants	Patients with knee OA diagnosed by clinical and radiological evidence with pain at rest for => 6 months. If bilateral, only the more painful knee was chosen. Previous medication for knee pain was abruptly stopped before treatment started. Number of patients finished this study: 26 Male/female: 15/21 Mean (SD) age: 66 (9.6), range 31-83 years
Interventions	Patients were assigned to receive 3 random sequences of 3 interventions: 1) TENS+drug placebo (AT) 2) naprosyn 250 mg bid+placebo TENS (AD) 3) placebo for both (PP) TENS device: 3M Tenzcare dual-channel stimulators Wave form: not available Pulse width: 100 microS Pulse frequency: 70 Amplitude: adjusted by the patients to reach the highest amplitude consistent with continuous confort Electrode placement: 4 acupuncture points: spleen 9, 10 and stomach 34, 35 Placebo: TENS device with an adaptor placed at the end of electrodes to prevent the current flow. Schedule: 30-60 minutes per session for => 3 sessions per day, continuously for 3 weeks
Outcomes	1) Patient's opinion of treatment efficacy (OTE) 2) VAS for pain relief 3) Pain index for the knee (PIK) 4) Daily VAS for pain (DVA) 5) Piper pain intensity scale (PPS)
Notes	Quality = 1 (R1, D0, W0)
Allocation concealment	B – Unclear

Study	**Lewis D 1984**
Methods	Randomized, double-blind, placebo controlled, crossover trial Sample size at entry: 30 Dropouts: 2 Treatment duration: 6 weeks (3weeks in each treatment)
Participants	Adult patients with definite diagnosis of knee OA with chronic knee pain for => 12 months Male/female: 8/22 Median age: 61 years (range 40-83) Median disease duration: 7.5 years (1-40)
Interventions	First "wash out" week: paracetamol only TENS device: portable, battery-operated RDG Tiger Pulse Stimulator Stimulation mode: conventional 4 siliconised rubber electrodes Electrode placement: around the painful knee at Chinese acupuncture points Placebo: broken contact at the jack-plug of electrode leads Treated time per session: 30-60 minutes Schedule of treatment: 3 times a day for 3 weeks

Characteristics of included studies (*Continued*)

	Total number of treatment sessions: 63
Outcomes	1) Pain relief (VAS) 2) Return count of paracetamol tablets 3) Duration of pain relief following each TENS treatment 4) Patient's opinions questionnaire 5) Pain index
Notes	Quality = 3 (R1, D1, W1)
Allocation concealment	B – Unclear

Study	**Smith 1983**
Methods	Randomized, single-blind, parallel, placebo controlled trial Sample size at entry: 32 Dropouts:2 Number of patients in each group: 15 Treatment duration: 4 weeks Follow up: at week 4 and 8
Participants	Patients with clinical diagnosis of OA with inclusion criteria: 1) OA knee is the only reason for referral to the physiotherapy department and the only source of pain 2) Age between 50 and 80 years 3) Receive no treatment for OA other than oral analgesics or NSAIDs for 2 months or less 4) No history of malignancy, inflammatory arthropathy, or knee operation 5) No cardiac pacemaker 6) No previous TENS treatment Male/female: 5/10, 5/10 Mean age in years (range): 65 (50-80), 70 (55-79)
Interventions	First 'standard' week without any treatment Treatment group: TENS device: Battery powered RDG Tiger Pulse Wave form: square Conventional mode Frequency: 32-50 Hz Pulse width: 80 microsecs Intensity and votage control: adjusted until a comfortable tingling sensation is felt Electrodes: 4 Electrode placements: on tender points around the knee and/or acupuncture points (spleen 9, xiyan and urinary bladder 40) Electrode jelly: Lec Tec pads Placebo: same device with a broken connection between the machine and electrodes at the output jack plug. A 5-10 Hz flashing red light at the device is used for visual reinforcement. Treatment duration: 20 minutes Number of sessions: 8 over 4 weeks
Outcomes	'Significant pain relief' defined as 1) Either a ten-point or 50% decrease in weekly pain score, measured on a seven-point daily pain scale, compared with the 'standard' week (max score 49, min 7) 2) A 50% decreases in analgesic intake compared with the 'standard' week. 3) A five-point improvement in the weekly sleep disturbance score, measured on a seven-point weekly scale, compared with the 'standard' week.

	If any two of these criteria are fulfilled and no worsening in the other, this means the patient benefits from treatment. If criteria 1 or 3 is fulfilled alone, and no worsening in any of the criteria, this also means the patient benefits from the treatment. Number of patients with significant pain relief at end point, at 8 weeks and immediate pain relief.
Notes	Quality = 3 (R2, D0, W1)
Allocation concealment	A – Adequate

Study	**Taylor 1981**
Methods	Randomized, double-blind, crossover, placebo controlled trial Sample size at entry: 12 Dropouts: 2 Study duration: 1 month Follow up: 1 year
Participants	Patients with clinical and radiological evidences of symptomatic knee OA with disability and were candidates for total knee replacement. If had bilateral knee OA, the more synptomatic knee was chosen to study. Exclusion: patients who did not complete the study, or with secondary cause of OA Male/female: 1/9 Mean age: 71.5 years Mean duration of disease: not available
Interventions	TENS device: standard dual output Gatron stimulators Wave form: not available Current, amplitude, and pulse width: adjusted by the patients to produce a " comfortable, firm, tingling" sensation by adjusting the amplitude first, then the pulse width and then the rate. Electrode placement: 1 each on the anterior, posterior, lateral, and medial sided of the painful knee Placebo: same devices with broken wires and an audio device with the arbitrary setting of the sound at voltage amplitude 7 and adjustable for a pleasant feeling. Treated time per session: 30-60 minutes Schedule of treatment: many times a day for 2 weeks
Outcomes	1) Subjective pain 0=no change in pain +1=some pain relief +2=marked pain relief +3=complete pain relief - 1= pain worse 2) Pain score 0=no change +1= pain improved by one degree in scale +2=pain improved by two degrees - 1=pain worse by one degree - 2=pain worse by two degrees 3) Ambulation

	0=no change +1=walking greater distance +2=walking unlimited
-	
	1=walking less distance 4) Pain medication 0=no change +1=taking less medication for pain +2=taking no medication
-	
	1=taking more medication
Notes	Quality = 2 (R1,D0,W1)
Allocation concealment	B – Unclear

Study	**Yurtkuran 1999**
Methods	Randomized, double-blind, parallel group, placebo controlled trial (double blind for AL-TENS vs placebo, for the other interventions, only single blinded.) Sample size at entry: 100 Dropouts:0 Number of patients in each group: 25 Treatment duration: 2 weeks Follow up: at week 2
Participants	Patients who fulfilled the following criteria: 1) duration of knee pain => 6 months 2) osteoarthritic radiological findings 3) no gross leg malalignment 4) no mechanical block to knee motion 5) no significant concomitant medical problem or bleeding tendency 6) not undergoing any specific medical or surgical treatment, or physical therapy 7) no cardiac pacemaker If both knees were equally painful, the right knee was chosen to study. Male/female: 9/91 (2/23, 4/21, 0/25, 3/22) Range of age 45-70 (45-70, 45-69, 45-69, 45-69) Disease duration: <1 to 40 years
Interventions	Four parallel groups: 1) TENS device: MEATENS with point detector model F-2 mode of stimulation: low frequency, high intensity, acupuncture-like TENS (AL-TENS) wave form: rectangular amplitude: 0.4 - 2.5 Volt, the current were increased to create muscle contraction but just below the pain tolerance threshold. pulse width: 1000 microsecs. pulse frequency: 4 Hz dual channel 4 rubber electrodes placement: SP-9, GB-34, ST-34, ST-35 2) Electroacupu ncture (EA) four stainless acupuncture needles (Seirin: 0.25x40mm) were inserted on pre-sterilized skin at the same four points as AL-TENS. Then the needles were connected to electrostimulator device with same settings.

	3) Ice message: a 10-cm piece of wood with a cube-shaped sponge attached at one end was dipped into the water and then frozen, then used to massage the four acupoints. If the patients experienced pain, treatment would be withheld for 3 minutes. 4) Placebo: used the same device as TENS but with a disconnected jack-plug. A glowing red light on the device was used instead. treatment time per session: 20 minutes schedule of treatment: once daily, five days a week for 2 weeks total number of treatment sessions: 10
Outcomes	1) Present Pain Intensity (PPI): overall pain intensity was measured on a 1-5 scale, mild = 1 moderate = 2 severe = 3 very severe = 4 excruciating = 5 2) Stiffness 3) 50-foot walking time in minutes 4) Quadriceps muscle strength 5) Active knee flexion
Notes	Quality = 3 (R1, D1, W1)
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Jensen JE 1985	Populations have post-knee surgery conditions.
Lundeberg 1984	Patients with myalgia, not OA.
Sternbach 1976	Population have mostly low back pain.
Zizic 1995	The device used was not considered a TENS device.

ANALYSES

Comparison 01. TENS/AL-TENS vs. placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain Relief (VAS)	6	264	Weighted Mean Difference (Fixed) 95% CI	-0.79 [-1.27, -0.30]
02 Knee stiffness	2	90	Weighted Mean Difference (Fixed) 95% CI	-6.02 [-9.07, -2.96]

Comparison 02. AL-TENS vs. placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain relief	1	50	Weighted Mean Difference (Fixed) 95% CI	-0.80 [-1.39, -0.21]
02 Stiffness of the knee	1	50	Weighted Mean Difference (Fixed) 95% CI	-7.90 [-11.18, -4.62]
03 50-foot walking time	1	50	Weighted Mean Difference (Fixed) 95% CI	-22.60 [-43.01, -2.19]
04 Quadriceps muscle strength	1	50	Weighted Mean Difference (Fixed) 95% CI	-5.20 [-7.85, -2.55]

05 Knee flexion	1	50	Weighted Mean Difference (Fixed) 95% CI	-11.30 [-17.59, -5.01]

Comparison 03. TENS vs. placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain Relief (VAS)	5	214	Weighted Mean Difference (Fixed) 95% CI	-0.75 [-1.63, 0.12]
02 Number of patients with pain improvement	5	201	Peto Odds Ratio 95% CI	3.91 [2.13, 7.17]

Comparison 04. TENS vs. placebo, follow up

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients with pain improvement	2	62	Peto Odds Ratio 95% CI	4.31 [1.55, 12.01]

Comparison 06. TENS vs. placebo, after one application

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain relief			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

Comparison 11. Subgroup analysis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain relief (VAS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Pain relief (VAS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
03 Pain relief VAS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
04 Pain relief VAS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

INDEX TERMS

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

MeSH check words

Humans

COVER SHEET

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Authors Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P, Wells G

Contribution of author(s)

Manathip Osiri extracted and analyzed data and wrote the manuscript.
Lucie Brosseau and Vivian Welch extracted data and edited early versions of the manuscript.
George Wells, Beverley Shea and Peter Tugwell contributed methodological expertise, content and editorial comments for the final drafts.
Jessie McGowan designed and conducted the electronic search strategy.

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Contact address	Dr Manathip Osiri Associate Professor, Division of Rheumatology Department of Medicine, Faculty of Medicine Chulalongkorn University 1873 Rama IV Road, Pathumwan Bangkok 10330 THAILAND E-mail: Manathip.O@chula.ac.th Tel: +662-256-4526 Fax: +662-252-8467
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 TENS/AL-TENS vs. placebo, Outcome 01 Pain Relief (VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 01 TENS/AL-TENS vs. placebo

Outcome: 01 Pain Relief (VAS)

Study	placebo		TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Fargas-Babjak 1989	18	10.72 (64.11)	19	56.05 (37.51)		0.0	-45.33 [-79.41, -11.25]
Grimmer 1992	20	2.80 (3.20)	20	4.90 (3.30)		5.8	-2.10 [-4.11, -0.09]
Lewis B 1994	31	43.20 (23.10)	28	48.10 (28.60)		0.1	-4.90 [-18.25, 8.45]
Lewis D 1984	29	4.80 (2.45)	29	5.50 (2.45)		14.9	-0.70 [-1.96, 0.56]
Taylor 1981	10	0.90 (1.90)	10	0.80 (1.60)		10.0	0.10 [-1.44, 1.64]
Yurtkuran 1999	25	0.20 (0.89)	25	1.00 (1.20)		69.1	-0.80 [-1.39, -0.21]
Total (95% CI)	133		131			100.0	-0.79 [-1.27, -0.30]

Test for heterogeneity chi-square=9.85 df=5 p=0.08 I^2 =49.3%

Test for overall effect z=3.16 p=0.002

Analysis 01.02. Comparison 01 TENS/AL-TENS vs. placebo, Outcome 02 Knee stiffness

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

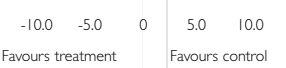
Comparison: 01 TENS/AL-TENS vs. placebo

Outcome: 02 Knee stiffness

Study	Placebo		TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Grimmer 1992	20	3.00 (6.40)	20	6.90 (7.90)		47.0	-3.90 [-8.36, 0.56]
Yurtkuran 1999	25	0.60 (5.87)	25	8.50 (8.96)		53.0	-7.90 [-12.10, -3.70]
Total (95% CI)	45		45			100.0	-6.02 [-9.07, -2.96]

Test for heterogeneity chi-square=1.64 df=1 p=0.20 I^2 =39.0%

Test for overall effect z=3.86 p=0.0001



Analysis 02.01. Comparison 02 AL-TENS vs. placebo, Outcome 01 Pain relief

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 02 AL-TENS vs. placebo

Outcome: 01 Pain relief

Study	placebo N	placebo Mean(SD)	TENS N	TENS Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Yurtkuran 1999	25	0.20 (0.89)	25	1.00 (1.20)		100.0	-0.80 [-1.39, -0.21]
Total (95% CI)	25		25			100.0	-0.80 [-1.39, -0.21]
Test for heterogeneity: not applicable							
Test for overall effect z=2.68 p=0.007							

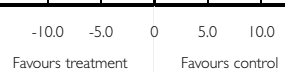
Analysis 02.02. Comparison 02 AL-TENS vs. placebo, Outcome 02 Stiffness of the knee

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 02 AL-TENS vs. placebo

Outcome: 02 Stiffness of the knee

Study	Placebo N	Placebo Mean(SD)	AL-TENS N	AL-TENS Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Yurtkuran 1999	25	0.60 (5.87)	25	8.50 (5.96)		100.0	-7.90 [-11.18, -4.62]
Total (95% CI)	25		25			100.0	-7.90 [-11.18, -4.62]
Test for heterogeneity: not applicable							
Test for overall effect z=4.72 p<0.00001							



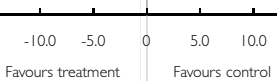
Analysis 02.03. Comparison 02 AL-TENS vs. placebo, Outcome 03 50-foot walking time

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 02 AL-TENS vs. placebo

Outcome: 03 50-foot walking time

Study	Placebo N	Placebo Mean(SD)	AL-TENS N	AL-TENS Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Yurtkuran 1999	25	5.60 (5.30)	25	28.20 (51.80)		100.0	-22.60 [-43.01, -2.19]
Total (95% CI)	25		25			100.0	-22.60 [-43.01, -2.19]
Test for heterogeneity: not applicable							
Test for overall effect z=2.17 p=0.03							



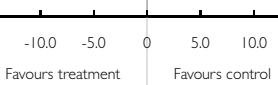
Analysis 02.04. Comparison 02 AL-TENS vs. placebo, Outcome 04 Quadriceps muscle strength

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 02 AL-TENS vs. placebo

Outcome: 04 Quadriceps muscle strength

Study	Placebo		AL-TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Yurtkuran 1999	25	-4.40 (6.40)	25	0.80 (2.20)		100.0	-5.20 [-7.85, -2.55]
Total (95% CI)	25		25			100.0	-5.20 [-7.85, -2.55]
Test for heterogeneity: not applicable							
Test for overall effect z=3.84 p=0.0001							



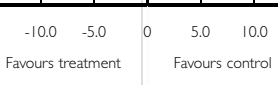
Analysis 02.05. Comparison 02 AL-TENS vs. placebo, Outcome 05 Knee flexion

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 02 AL-TENS vs. placebo

Outcome: 05 Knee flexion

Study	Placebo		AL-TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Yurtkuran 1999	25	-2.40 (11.70)	25	8.90 (10.99)		100.0	-11.30 [-17.59, -5.01]
Total (95% CI)	25		25			100.0	-11.30 [-17.59, -5.01]
Test for heterogeneity: not applicable							
Test for overall effect z=3.52 p=0.0004							



Analysis 03.01. Comparison 03 TENS vs. placebo, Outcome 01 Pain Relief (VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

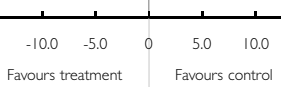
Comparison: 03 TENS vs. placebo

Outcome: 01 Pain Relief (VAS)

Study	placebo N	placebo Mean(SD)	TENS N	TENS Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Fargas-Babjak 1989	18	10.72 (64.11)	19	56.05 (37.51)		0.1	-45.33 [-79.41, -11.25]
Grimmer 1992	20	2.80 (3.20)	20	4.90 (3.30)		18.9	-2.10 [-4.11, -0.09]
Lewis B 1994	31	43.20 (23.10)	28	48.10 (28.60)		0.4	-4.90 [-18.25, 8.45]
Lewis D 1984	29	4.80 (2.45)	29	5.50 (2.45)		48.2	-0.70 [-1.96, 0.56]
Taylor 1981	10	0.90 (1.90)	10	0.80 (1.60)		32.4	0.10 [-1.44, 1.64]
Total (95% CI)	108		106			100.0	-0.75 [-1.63, 0.12]

Test for heterogeneity chi-square=9.85 df=4 p=0.04 I^2 =59.4%

Test for overall effect z=1.69 p=0.09



Analysis 03.02. Comparison 03 TENS vs. placebo, Outcome 02 Number of patients with pain improvement

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 03 TENS vs. placebo

Outcome: 02 Number of patients with pain improvement

Study	TENS n/N	placebo n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Fargas-Babjak 1989	14/19	5/18		22.7	5.98 [1.67, 21.33]
Lewis B 1994	7/29	2/29		18.5	3.64 [0.89, 14.91]
Lewis D 1984	12/28	4/28		27.8	3.96 [1.25, 12.48]
Smith 1983	10/15	4/15		18.5	4.73 [1.15, 19.38]
Taylor 1981	6/10	5/10		12.5	1.47 [0.26, 8.18]
Total (95% CI)	101	100		100.0	3.91 [2.13, 7.17]

Total events: 49 (TENS), 20 (placebo)

Test for heterogeneity chi-square=1.76 df=4 p=0.78 I^2 =0.0%

Test for overall effect z=4.41 p=0.00001

Analysis 04.01. Comparison 04 TENS vs. placebo, follow up, Outcome 01 Number of patients with pain improvement

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 04 TENS vs. placebo, follow up

Outcome: 01 Number of patients with pain improvement

Study	TENS n/N	placebo n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Fargas-Babjak 1989	9/15	2/17		50.7	7.94 [1.88, 33.46]
Smith 1983	7/15	4/15		49.3	2.30 [0.53, 9.90]
Total (95% CI)	30	32		100.0	4.31 [1.55, 12.01]
Total events: 16 (TENS), 6 (placebo)					
Test for heterogeneity chi-square=1.40 df=1 p=0.24 I^2 =28.7%					
Test for overall effect z=2.79 p=0.005					

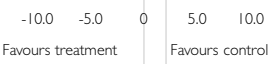
Analysis 06.01. Comparison 06 TENS vs. placebo, after one application, Outcome 01 Pain relief

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 06 TENS vs. placebo, after one application

Outcome: 01 Pain relief

Study	Placebo N	Placebo Mean(SD)	TENS N	TENS Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Strong Burst Mode TENS vs. Placebo							
Grimmer 1992	20	2.80 (3.20)	20	4.40 (1.80)		100.0	-1.60 [-3.21, 0.01]
Subtotal (95% CI)	20		20			100.0	-1.60 [-3.21, 0.01]
Test for heterogeneity: not applicable							
Test for overall effect z=1.95 p=0.05							
02 High Rate TENS vs. Placebo							
Grimmer 1992	20	2.80 (3.20)	20	4.90 (3.30)		100.0	-2.10 [-4.11, -0.09]
Subtotal (95% CI)	20		20			100.0	-2.10 [-4.11, -0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=2.04 p=0.04							

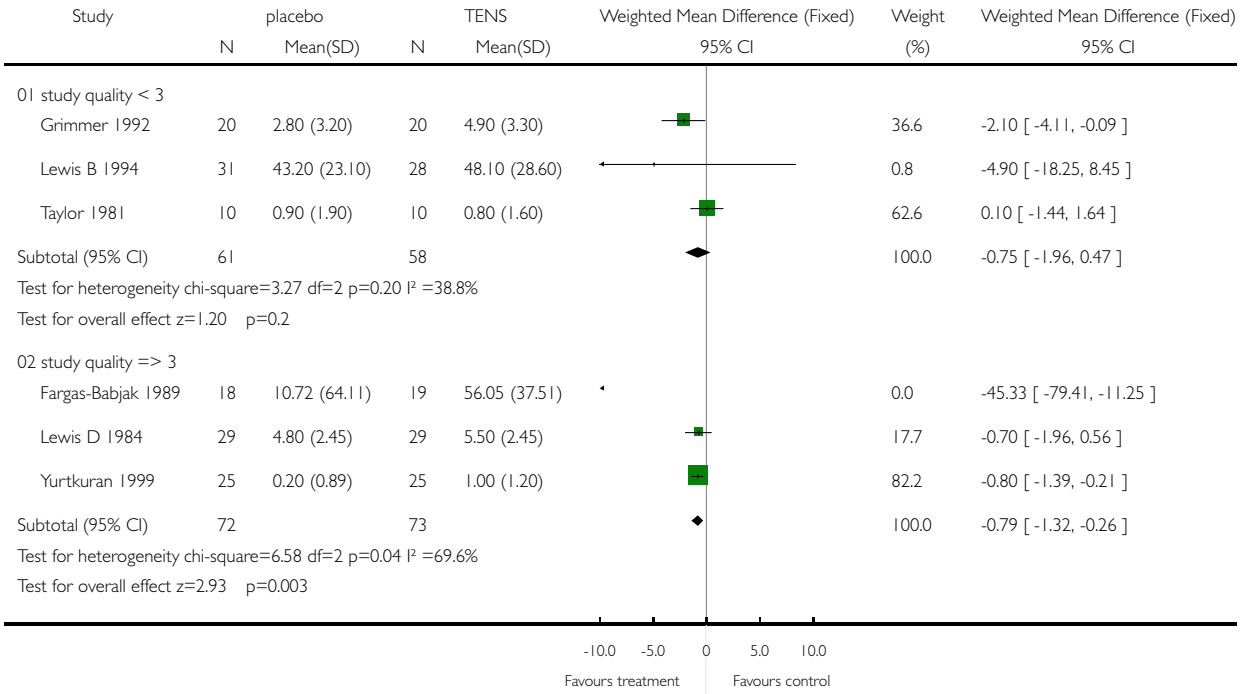


Analysis 11.01. Comparison 11 Subgroup analysis, Outcome 01 Pain relief (VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 11 Subgroup analysis

Outcome: 01 Pain relief (VAS)

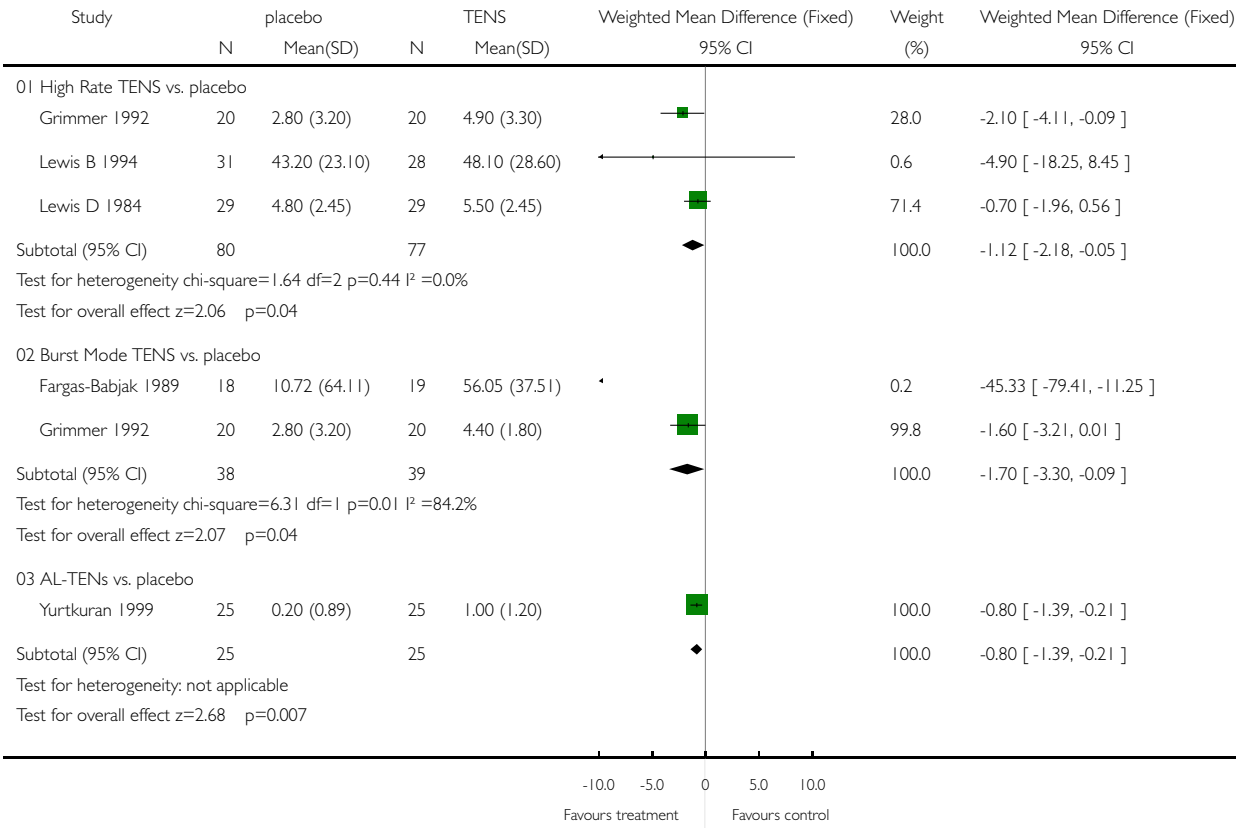


Analysis 11.02. Comparison 11 Subgroup analysis, Outcome 02 Pain relief (VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 11 Subgroup analysis

Outcome: 02 Pain relief (VAS)



Analysis 11.03. Comparison 11 Subgroup analysis, Outcome 03 Pain relief VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 11 Subgroup analysis

Outcome: 03 Pain relief VAS)

Study	placebo		TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 Single application							
Grimmer 1992	20	2.80 (3.20)	20	4.90 (3.30)		100.0	-2.10 [-4.11, -0.09]
Subtotal (95% CI)	20		20			100.0	-2.10 [-4.11, -0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=2.04 p=0.04							
02 Repeated applications							
Fargas-Babjak 1989	18	10.72 (64.11)	19	56.05 (37.51)		0.0	-45.33 [-79.41, -11.25]
Lewis B 1994	31	43.20 (23.10)	28	48.10 (28.60)		0.1	-4.90 [-18.25, 8.45]
Lewis D 1984	29	4.80 (2.45)	29	5.50 (2.45)		15.8	-0.70 [-1.96, 0.56]
Taylor 1981	10	0.90 (1.90)	10	0.80 (1.60)		10.6	0.10 [-1.44, 1.64]
Yurtkuran 1999	25	0.20 (0.89)	25	1.00 (1.20)		73.4	-0.80 [-1.39, -0.21]
Subtotal (95% CI)	113		111			100.0	-0.70 [-1.21, -0.20]
Test for heterogeneity chi-square=8.12 df=4 p=0.09 I^2 =50.7%							
Test for overall effect z=2.75 p=0.006							

Analysis 11.04. Comparison 11 Subgroup analysis, Outcome 04 Pain relief VAS)

Review: Transcutaneous electrical nerve stimulation for knee osteoarthritis

Comparison: 11 Subgroup analysis

Outcome: 04 Pain relief VAS)

Study	placebo		TENS		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 Studies with TENS application less than 4 weeks							
Grimmer 1992	20	2.80 (3.20)	20	4.90 (3.30)		18.9	-2.10 [-4.11, -0.09]
Lewis B 1994	31	43.20 (23.10)	28	48.10 (28.60)		0.4	-4.90 [-18.25, 8.45]
Lewis D 1984	29	4.80 (2.45)	29	5.50 (2.45)		48.3	-0.70 [-1.96, 0.56]
Taylor 1981	10	0.90 (1.90)	10	0.80 (1.60)		32.4	0.10 [-1.44, 1.64]
Subtotal (95% CI)	90		87			100.0	-0.72 [-1.60, 0.15]
Test for heterogeneity chi-square=3.27 df=3 p=0.35 I^2 =8.2%							
Test for overall effect z=1.62 p=0.1							
02 Studies with TENS application at least 4 weeks							
Fargas-Babjak 1989	18	10.72 (64.11)	19	56.05 (37.51)		100.0	-45.33 [-79.41, -11.25]
Subtotal (95% CI)	18		19			100.0	-45.33 [-79.41, -11.25]
Test for heterogeneity: not applicable							
Test for overall effect z=2.61 p=0.009