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ARTIKEL TINJAUAN PUSTAKA

EFFECTIVENESS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION FOR PAIN IN KNEE OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

EFEKTIVITAS TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION TERHADAP NYERI OSTEOARTRITIS LUTUT: TELAAH SISTEMATIS DAN META-ANALISIS

Robby Soetedjo, **Erlangga Saputra Arifin*, Jason Adiwardhana, Richard Wijaya**

Fakultas Kedokteran dan Ilmu Kesehatan Universitas Katolik Indonesia Atma Jaya, Jl. Pluit Raya No. 2, Jakarta 14440
*** Korespondensi:** arifinerlangga@gmail.com

ABSTRAK
Pendahuluan: Osteoartritis (OA) lutut merupakan salah satu penyebab penting nyeri kronik dan disabilitas. Transcutaneous electrical nerve stimulation (TENS) merupakan pilihan analgesik nonfarmakologis, tetapi efektivitasnya masih belum pasti. Telaah sistematis dan meta-analisis ini mengevaluasi efektivitas dan keamanan TENS pada OA lutut.
Metode: PubMed, ScienceDirect, EBSCO, ProQuest, dan ClinicalTrials.gov ditelusuri sejak awal basis data hingga 9 Maret 2021 tanpa pembatasan bahasa atau tahun publikasi. Uji acak terkontrol yang membandingkan TENS dengan kelompok kontrol diikutsertakan. Risiko bias dinilai menggunakan RoB 2, kepastian bukti menggunakan GRADE, dan luaran digabungkan dengan model random-effects serta penyesuaian Hartung-Knapp.
Hasil: Dari 335 rekod yang teridentifikasi, 11 uji acak terkontrol memenuhi kriteria telaah kualitatif dan delapan berkontribusi pada meta-analisis nyeri. Risiko bias keseluruhan rendah pada empat studi, menimbulkan beberapa kekhawatiran pada empat studi, dan tinggi pada tiga studi. TENS menunjukkan arah penurunan nyeri, tetapi estimasi gabungan masih tidak presisi (Hedges g -0,53; 95% CI -1,24 hingga 0,18; I^2=76%). Perbedaan fungsi juga tidak presisi (MD -3,74; 95% CI -9,77 hingga 2,29), demikian pula kejadian tidak diinginkan (RR 0,65; 95% CI 0,23 hingga 1,80).
Simpulan: Estimasi gabungan mengarah pada kemungkinan manfaat TENS terhadap nyeri dan fungsi pada OA lutut, tetapi bukti masih tidak presisi dan heterogen. Diperlukan uji acak terkontrol dengan sham yang lebih ketat dan memadai serta pembaruan sintesis bukti.
Kata Kunci: meta-analisis, nyeri, osteoartritis lutut, stimulasi saraf listrik transkutan, telaah sistematis

ABSTRACT
Introduction: *Knee osteoarthritis (OA) is a common cause of chronic pain and disability. Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological analgesic option, but its efficacy remains uncertain. This systematic review and meta-analysis evaluated the effectiveness and safety of TENS in knee OA.*
Methods: *PubMed, ScienceDirect, EBSCO, ProQuest, and ClinicalTrials.gov were searched from database inception to 9 March 2021 without language or publication-date restrictions. Randomized controlled trials comparing TENS with a control were eligible. Risk of bias was assessed using RoB 2, certainty of evidence using GRADE, and outcomes were pooled using random-effects models with Hartung-Knapp adjustment.*
Results: *Of 335 records identified, 11 randomized controlled trials met the qualitative inclusion criteria and eight contributed to the pain meta-analysis. Overall risk of bias was low in four studies, raised some concerns in four, and high in three. TENS showed a directionally lower pain score, but the pooled effect was imprecise (Hedges g -0.53, 95% CI -1.24 to 0.18; I^2=76%). Function also showed an imprecise difference (MD -3.74, 95% CI -9.77 to 2.29), as did adverse events (RR 0.65, 95% CI 0.23 to 1.80).*
Conclusion: *Pooled estimates suggest a possible benefit of TENS for knee OA pain and function, but the evidence is imprecise and heterogeneous. More rigorous, adequately powered sham-controlled trials and an updated evidence synthesis are required.*
Key Words: *knee osteoarthritis, meta-analysis, pain, systematic review, transcutaneous electrical nerve stimulation*

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative joint disorder characterized by progressive structural changes involving articular cartilage, subchondral bone, synovium, and other periarticular tissues.[1] The knee is one of the most commonly affected joints, and symptomatic knee OA contributes substantially to pain, stiffness, activity limitation, and reduced health-related quality of life.[2] A global synthesis estimated that approximately 654 million adults aged 40 years or older had knee OA in 2020, underscoring its considerable population burden.[3] Although OA is not usually associated with high mortality, its chronic symptoms and functional consequences can markedly impair quality of life.[4]

Management of knee OA is primarily directed toward symptom control, preservation of function, and reduction of disability because no established therapy reliably reverses the disease process.[5] Non-pharmacological measures and analgesic or anti-inflammatory drugs are commonly used, while surgery is reserved for selected patients with advanced disease and persistent symptoms.[5-7] Nonsteroidal anti-inflammatory drugs can provide meaningful pain relief but may be limited by gastrointestinal, cardiovascular, and renal adverse effects, particularly in susceptible patients.[7,8] Consequently, safe non-pharmacological adjuncts remain clinically relevant.

Transcutaneous electrical nerve stimulation (TENS) delivers electrical impulses through surface electrodes to modulate nociceptive processing and is attractive because it is non-invasive and can be administered without systemic drug exposure.[9,10,26] However, previous reviews have reported inconsistent conclusions, partly because trials differ in stimulation frequency, pulse width, session duration, treatment course, comparator, co-interventions, and outcome timing.[9,10] Therefore, this systematic review and meta-analysis aimed to critically evaluate the effectiveness and safety of TENS for pain and functional outcomes in patients with knee OA.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted using the Cochrane Handbook for Systematic Reviews of Interventions version 6.2 as methodological guidance and is reported in accordance with the PRISMA 2020 statement.[11,12]

Five electronic sources were searched: PubMed, ScienceDirect, EBSCO, ProQuest, and ClinicalTrials.gov. The search combined terms for knee osteoarthritis and transcutaneous electrical nerve stimulation. No restrictions on language or publication year were applied. The searches were completed on 9 March 2021. Database-specific search strings and yields are presented in Table 1.

Search results were imported into EndNote X9 and duplicates were removed. Three reviewers (RS, RW, and JA) independently screened titles and abstracts, followed by full-text assessment of potentially eligible reports. Relevant information was recorded in a predefined extraction form. Disagreements regarding study eligibility were resolved by consensus among the review team.

Table 1. Search Keywords

Databases	Key Words	Articles
PubMed	("Osteoarthritis, Knee"[Mesh] OR "Knee Osteoarthritides" [Title/Abstract] OR "Knee Osteoarthritis"[Title/Abstract] OR "Osteoarthritis of Knee"[Title/Abstract] OR "Osteoarthritis of the Knee"[Title/Abstract]) AND ("Transcutaneous Electric Nerve Stimulation"[MeSH Terms] OR "Transcutaneous Electric Stimulation"[Title/Abstract] OR "Percutaneous Electric Nerve Stimulation"[Title/Abstract] OR "Percutaneous Electrical Nerve Stimulation"[Title/Abstract] OR "Transcutaneous Electrical Nerve Stimulation"[Title/Abstract] OR "TENS"[Title/Abstract] OR "Transdermal Electrostimulation"[Title/Abstract] OR "Percutaneous Neuromodulation Therapy"[Title/Abstract] OR "Percutaneous Electrical Neuromodulation"[Title/Abstract] OR "Analgesic Cutaneous Electrostimulation"[Title/Abstract] OR Electroanalgesia [Title/Abstract] OR Electroanalgesias[Title/Abstract])	205
ProQuest	ab("Knee Osteoarthritides" OR "Knee Osteoarthritis" OR "Osteoarthritis of Knee" OR "Osteoarthritis of the Knee") AND ab("Transcutaneous Electric Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR "Percutaneous Electrical Nerve Stimulation" OR "Transcutaneous Electrical Nerve Stimulation" OR "TENS" OR "Transdermal Electrostimulation" OR "Percutaneous Neuromodulation Therapy" OR "Percutaneous Electrical Neuromodulation" OR "Analgesic Cutaneous Electrostimulation" OR Electroanalgesia OR Electroanalgesias)	42
ScienceDirect	("Knee Osteoarthritides" OR "Knee Osteoarthritis" OR "Osteoarthritis of Knee" OR "Osteoarthritis of the Knee") AND ("Transcutaneous Electric Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR "Percutaneous Electrical Nerve Stimulation" OR "Transcutaneous Electrical Nerve Stimulation")	18
EBSCO	AB ("Knee Osteoarthritides" OR "Knee Osteoarthritis" OR "Osteoarthritis of Knee" OR "Osteoarthritis of the Knee") AND AB ("Transcutaneous Electric Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR “Percutaneous Electrical Nerve Stimulation” OR “Transcutaneous Electrical Nerve Stimulation” OR “TENS” OR "Transdermal Electrostimulation" OR "Percutaneous Neuromodulation Therapy" OR "Percutaneous Electrical Neuromodulation" OR "Analgesic Cutaneous Electrostimulation" OR Electroanalgesia OR Electroanalgesias)	4
ClinicalTrials.gov	"Knee Osteoarthritides" OR "Knee Osteoarthritis" OR "Osteoarthritis of Knee" OR "Osteoarthritis of the Knee" | "Transcutaneous Electric Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR “Percutaneous Electrical Nerve Stimulation” OR “Transcutaneous Electrical Nerve Stimulation”	26

Studies were eligible if they: (a) used TENS as the principal intervention; (b) included participants with knee OA of any reported radiographic or clinical severity; and (c) included a comparator group. Pain was the prespecified primary outcome, while additional clinical outcomes were permitted. Single-arm studies and feasibility studies without an eligible randomized comparator were excluded. Trials with co-interventions were eligible only when the co-intervention was balanced between the TENS and comparator groups. Reports were also excluded when the full text or data required for eligibility assessment could not be obtained.

When key study details were unclear, the

the authors were contacted for clarification. If essential eligibility or outcome information could not be confirmed, the study was not included in the relevant quantitative synthesis. For this review, TENS was defined as transcutaneous delivery of electrical impulses intended to modulate pain in knee OA.

Data extracted from each study included: (1) first author and publication year; (2) study characteristics, including design, location, intervention, and comparator; (3) participant characteristics, including sample size and Kellgren-Lawrence grade when available; and (4) reported outcomes. Pain was the primary outcome; function and adverse events were secondary outcomes.

Risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), which evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result.[13] Each study was categorized as low risk of bias, some concerns, or high risk according to RoB 2 guidance. Assessments were performed in pairs (RS and ESA), and disagreements were resolved through review-team discussion.

Certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and classified as high, moderate, low, or very low.[14]

Continuous outcomes measured on different scales were pooled as standardized mean differences (SMDs); outcomes reported on a common scale were pooled as mean differences (MDs). Inverse-variance random-effects models with Hartung-Knapp adjustment were used. Where necessary, standardized effects were expressed as Hedges g. Continuous data were entered as mean and standard deviation (SD); study authors were contacted when required summary data were unavailable. Binary outcomes were pooled as risk ratios (RRs) using the Mantel-Haenszel method.

Meta-analysis was performed in R version 4.0.4. Clinical and methodological heterogeneity was expected a priori; therefore, random-effects models were used. Statistical heterogeneity was assessed using Cochran's Q and I^2, interpreted approximately as 0-40% (might not be important), 30-60% (moderate), 50-90% (substantial), and 75-100% (considerable). Exploratory subgroup analyses, meta-regression, and leave-one-out sensitivity analyses were conducted when data allowed. Funnel-plot inspection and Egger's test were planned when at least 10 studies were available for an outcome. A two-sided p value <0.05 was considered statistically significant.

RESULTS

The electronic search identified 335 records. After duplicate removal, 225 records remained for title and abstract screening. Forty-one reports were assessed in full text, and 11 randomized controlled trials met the qualitative inclusion criteria.[15-25] Eight studies contributed to the quantitative synthesis of pain. Three studies did not contribute to that pooled estimate because the intervention or

outcome was considered incompatible with the prespecified quantitative analysis or because required summary statistics were unavailable. The study-selection process is shown in Figure 1.

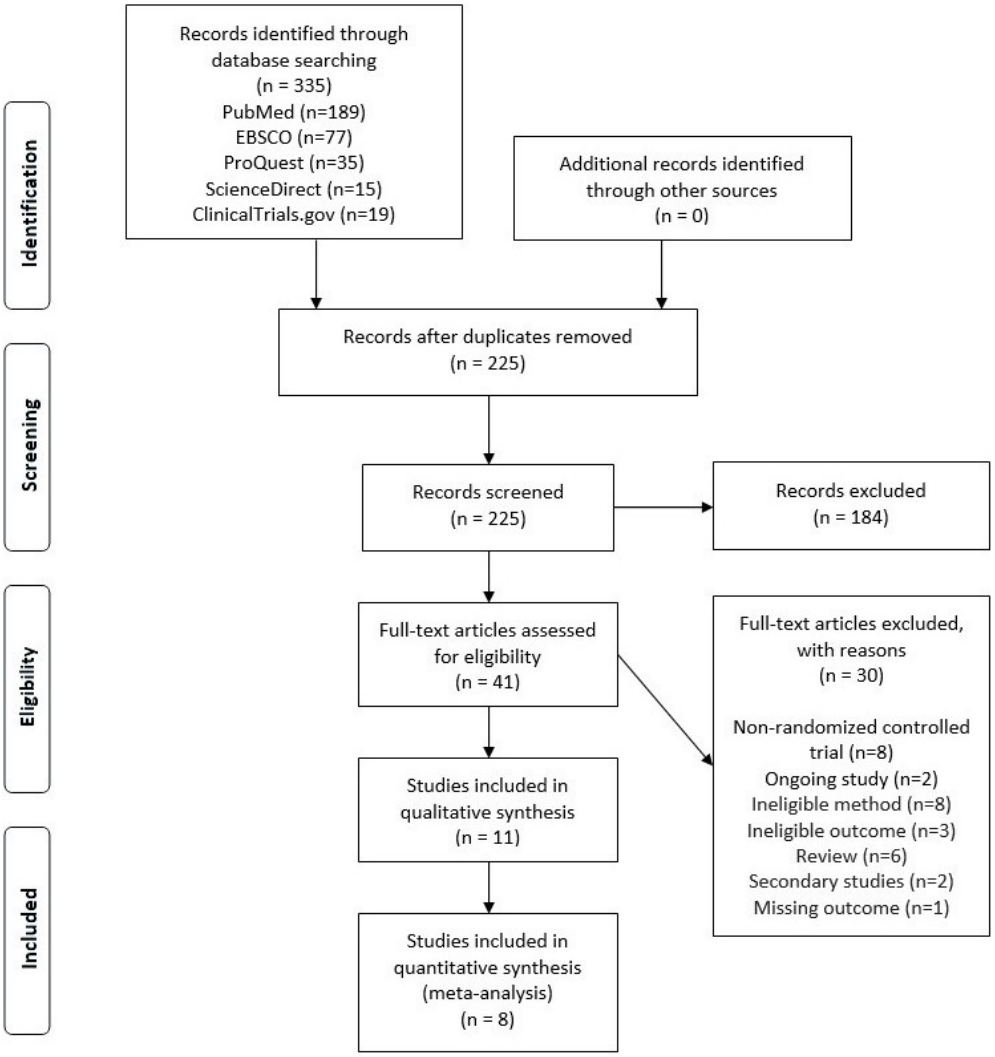

Figure 1. PRISMA flow diagram of the identification and selection of studies included in the analysis.

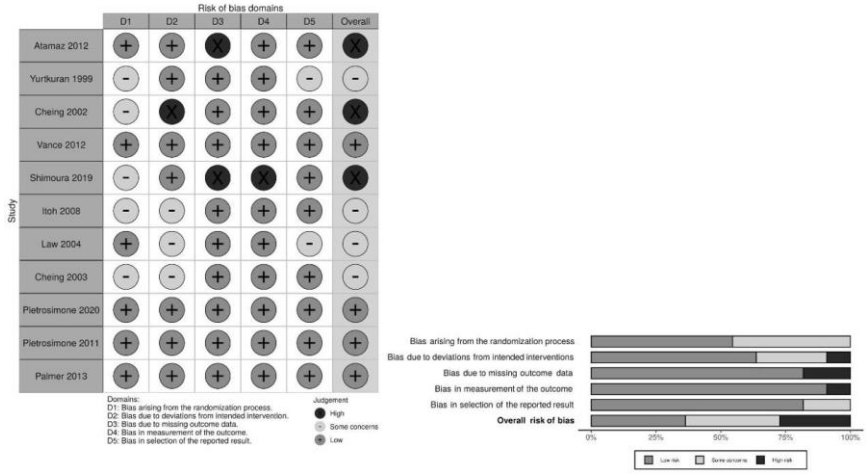

Figure 2. Risk of bias summary: review authors' judgements on risk of bias item for the included studies.

Table 2. Characteristics of the Included Studies

Author, Year	Location	Sample	Mean Age	Patient	Interventions		Measured Outcomes	Assessment time
					Interventions	Control		
Cheing, 2003	Hong Kong	N=38	65.5	Knee OA Kellgren-Lawrence grade 2 or above	TENS frequency of 100 Hz with a pulse width of 200 μs given for 20, 40, and 60 minutes (5 days a week for 2 weeks)	Sham TENS	VAS	Baseline, 5, 10 days, and 2 weeks after end of treatment (follow-up session)
Cheing, 2002	Hong Kong	N=32	64.7	Knee OA Kellgren-Lawrence grade 2 or above	TENS frequency of 80 Hz with a pulse width of 140 μs given for 60 minutes.	Sham TENS	VAS	4 weeks after treatment termination
Palmer, 2014	UK	N=147	61.05	Knee OA confirmed by ACR clinical criteria	TENS frequency of 110 Hz with a pulse width of 50 μs, Exercise (30 minutes education and group exercise)	Sham TENS + Exercise	WOMAC pain, WOMAC total	3, 6 (main outcome), 12, 24 weeks
Vance, 2012	USA	N=75	56.5	Medial compartment knee OA (radiographic and symptomatic)	HF-TENS (100 Hz) and LF-TENS (4 Hz) with pulse width of 100 μs for 20 minutes	Sham TENS	VAS during rest, VAS during TUG	Immediately
Shimoura, 2019	Japan	N=50	58.5	Knee OA Kellgren-Lawrence grade of 0 and 1	TENS frequency of 1 to 250 Hz with a pulse width of 60 μs	Sham TENS	VAS (Stair climb, TUG, 6MWT)	Immediately
Atamaz, 2012	Turkey	N=62	61.3	Knee OA Kellgren-Lawrence grade of 2 or 3	TENS at 80 Hz for 20 minutes, 5 sessions/week for 3 weeks	Sham TENS	VAS pain, WOMAC pain	Baseline, 1, 3, and 6 months
Yurtkuran, 1999	Turkey	N=50	53.12	Knee pain of 6 months or more and Knee OA radiologic finding	TENS was administered at a frequency of 4 Hz for 20 minutes (five days per week for 2 weeks)	Sham TENS	PPI	Immediately
Pietrosimone, 2011	USA	N=20	N/A	Knee OA Kellgren-Lawrence score between 1 and 4	TENS frequency of 150 Hz with a pulse width of 150 μs and exercise (three times per week for 4 weeks)	Sham TENS + Exercise	WOMAC pain, WOMAC total	Baseline, 2, and 4 weeks
Pietrosimone, 2020	USA	N=52	61	Knee OA Kellgren Lawrence score between 2-4	TENS at 150 Hz with a 150 μs pulse width plus 10 exercise sessions over 28 days	Sham TENS + Exercise	WOMAC (Pain, Stiffness, Function)	Baseline, Post 1 (4 Weeks), Post 2 (8 Weeks)
Itoh, 2008	Japan	N=12	62-83	Knee OA (clinical and radiographic diagnosis)	TENS-only arm: premixed amplitude-modulated stimulation at 122 Hz for 15 minutes, once weekly for 5 treatments	No specific intervention (topical poultice permitted if necessary)	VAS, WOMAC total	VAS: Baseline, 1, 2, 3, 4, 5, and 10 weeks WOMAC: Baseline, 5, and 10 weeks
Law, 2004	Hong Kong	N=34	82.55	Knee OA Kellgren-Lawrence grade ≥2	TENS at 2 Hz, 100 Hz, or alternating 2/100 Hz; pulse width 576 μs at 2 Hz and 200 μs at 100 Hz; 40 minutes/session, 5 days/week for 2 weeks	Sham TENS	VAS	Baseline, day 5, day 10, and 2 weeks after treatment

Abbreviations: 6MWT, 6 minute walk test; ACR, American College of Rheumatology; HF, high frequency; Hz, hertz; LF, low frequency; μs, microsecond; N/A, not available; OA, osteoarthritis; PPI, present pain intensity; TENS, transcutaneous electrical nerve stimulation; TUG, timed up and go; UK, United Kingdom; USA, United State of America; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Sample sizes refer to the intervention/comparator arms relevant to this review and may therefore be smaller than the total randomized sample of the original trial.

All 11 included studies used randomized controlled designs. Studies were conducted in Asia (Hong Kong, Japan, and Turkey), North America (United States), and Europe (United Kingdom). TENS protocols varied substantially in stimulation frequency, pulse width, session duration, treatment course, use of co-interventions, and timing of outcome assessment. Characteristics of the included studies are summarized in Table 2.

Across the five RoB 2 domains, concerns were identified in several studies. For the overall risk-of-bias judgment, four studies were rated low risk, four had some concerns, and three were rated high risk. The domain-level and overall judgments are summarized in Figure 2.

Table 3. Summary of findings

TENS compared to Control for Knee Osteoarthritis

Patient or population: Knee Osteoarthritis
Setting:
Intervention: TENS
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with TENS				
Pain assessed with: WOMAC pain and VAS	-	SMD 0.53 SD lower (1.24 lower to 0.18 higher)	-	366 (8 RCTs)	⊕⊕◯◯ LOW	TENS may reduce pain, but the estimate is imprecise and includes no effect.
Function assessed with: WOMAC	-	MD 3.74 points lower (9.77 lower to 2.29 higher)	-	179 (3 RCTs)	⊕⊕◯◯ LOW	TENS may result in little to no difference in function; the estimate is imprecise.
Number of patients experiencing any adverse event	41 per 1000	**27 per 1,000** (9 to 73)	**RR 0.65** (0.23 to 1.80)	416 (8 RCTs)	⊕⊕⊕◯ MODERATE	The effect of TENS on adverse events is uncertain because the confidence interval includes both benefit and harm.

*__The risk in the intervention group__ (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).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, risk ratio; SD, standard deviation; SMD, standardized mean difference; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

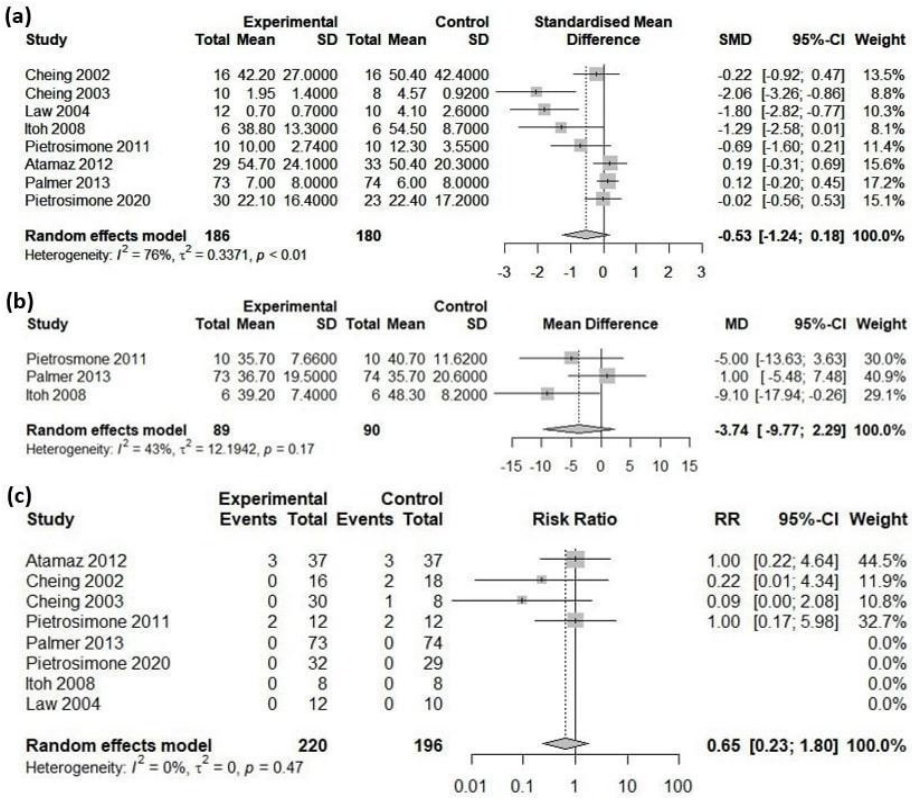

Figure 3. Forest plot depicting the
(a) standardized mean difference of pain reduction between TENS and control,
(b) mean difference of function between TENS and control, and
(c) risk ratio of adverse event between TENS and control.

Pain was the primary outcome. Studies measured pain using the Visual Analog Scale (VAS), the WOMAC pain subscale, or Present Pain Intensity (PPI). Because the instruments and scoring ranges differed, the primary quantitative synthesis used a standardized effect measure. Individual studies generally reported effects favoring TENS, but interpretation was based on the pooled estimate and its confidence interval rather than on within-study statistical significance alone. The GRADE summary is presented in Table 3.

The pooled analysis showed a moderate effect estimate in the direction of lower pain with TENS, but the 95% confidence interval included no effect (Hedges g -0.53, 95% CI -1.24 to 0.18; Figure 3a). Heterogeneity was substantial (I^2=76%; p for heterogeneity <0.01). Exploratory subgroup analyses by study location, comparator, and risk of bias did not provide a consistent explanation for the heterogeneity. The test for differences across risk-of-bias subgroups was not statistically significant (p=0.2145; Figure 4).

Random-effects meta-regression did not identify a statistically significant association between publication year and the SMD (Figure 5a). Leave-one-out sensitivity analysis indicated that the pooled estimate and heterogeneity were materially influenced by two studies with large effect estimates.[16,19] Omitting these studies reduced both the effect magnitude and heterogeneity, indicating that the primary pooled result was not robust to influential-study removal (Figure 5b).

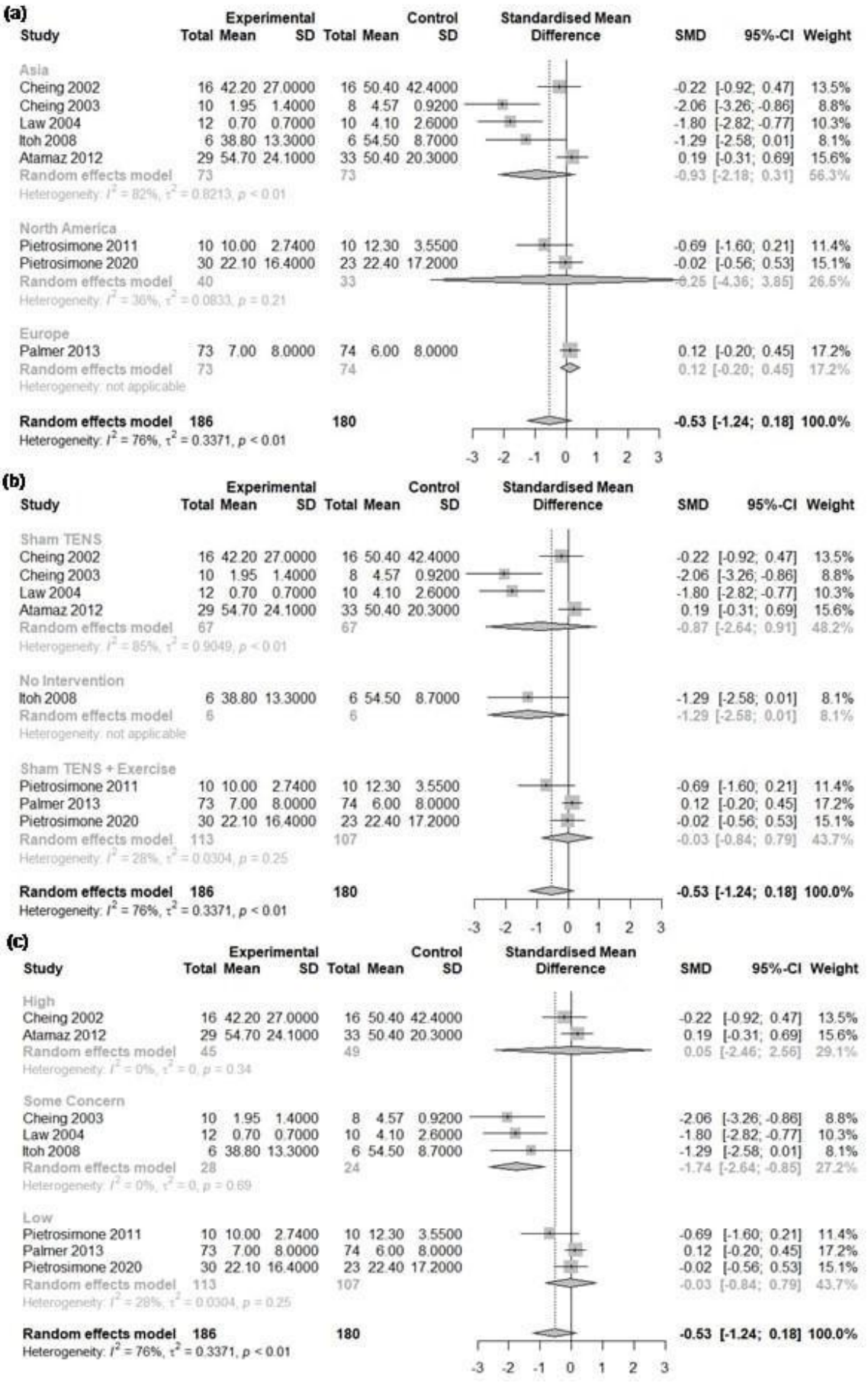

Figure 4. Subgroup analysis for pain outcome based on:
(a) location, (b) control used in the study, and (c) risk of bias.

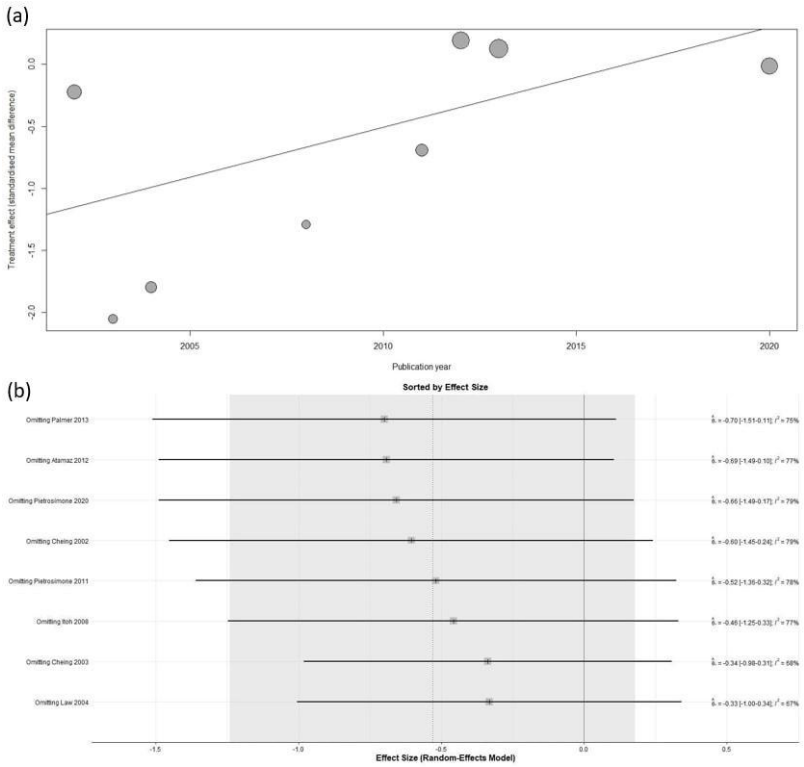

Figure 5. Visualization of
(a) meta-regression of relationship between pain reduction SMD and publication year depicted in bubble plot and (b) leave-one-out sensitivity analysis for pain reduction.

Function and stiffness were evaluated as secondary outcomes, most commonly using the WOMAC instrument. Three studies contributed to the pooled function analysis. The pooled estimate favored TENS but was imprecise and compatible with no difference (MD -3.74, 95% CI -9.77 to 2.29; Figure 3b). Accordingly, the certainty of evidence for functional improvement was rated low in the summary of findings (Table 3).

Adverse events were infrequently reported. The pooled RR was 0.65 (95% CI 0.23 to 1.80; Figure 3c), indicating an uncertain difference between TENS and control because the confidence interval included both potential benefit and potential harm. Reported events were mainly related to worsening OA symptoms rather than serious TENS-related complications. Publication bias was not assessed with funnel plots or Egger's test because fewer than 10 studies contributed to each pooled outcome.

DISCUSSION

This systematic review found that TENS produced an effect estimate in the direction of lower knee OA pain, but the pooled 95% confidence interval crossed the null and heterogeneity was substantial. Function showed a similar pattern: the point estimate favored TENS, yet the interval estimate was wide and compatible with little or no difference. The adverse-event estimate was also imprecise and should not be interpreted as evidence of a protective effect. Taken together, the results suggest possible clinical benefit but do not establish a statistically conclusive or precisely estimated treatment effect. This

distinction is important because several individual trials reported favorable results, whereas the pooled analysis incorporates between-study variability and provides a more appropriate basis for inference.

Several sources of clinical and methodological heterogeneity are evident. Included studies used a broad range of stimulation frequencies, pulse widths, session durations, treatment courses, and assessment times. Some evaluated TENS as a stand-alone intervention, whereas others used the same exercise program in both trial arms or included other co-interventions. Participant characteristics also varied in radiographic severity and symptom profile. Pain was measured using VAS, WOMAC pain, or PPI; although these are established pain measures, their different scales necessitated use of standardized effects for pooled pain analysis.[27] Standardization addresses differences in measurement units, but it does not remove heterogeneity related to treatment dose, population, comparator credibility, or follow-up timing.

The current data do not justify a firm conclusion regarding an optimal TENS dose or treatment duration. Immediate effects were assessed in some trials, whereas others evaluated outcomes after repeated treatment over several weeks.[16-19,22,25] Such differences may influence observed effect sizes. Mechanistically, TENS may modulate nociceptive signaling through peripheral and central pathways, but physiological plausibility alone does not establish clinical efficacy.[26] Therefore, apparent differences between stimulation protocols should be regarded as hypothesis-generating unless supported by adequately powered head-to-head comparisons or prespecified dose-response analyses.

The findings should also be interpreted in the context of evolving evidence. Earlier syntheses reported uncertainty or heterogeneity regarding transcutaneous electrical stimulation for knee OA.[9,10] A later systematic review and meta-analysis published in 2022 included 14 trials and reported improvements in pain and function, while a 2026 dose-response meta-analysis incorporated 36 trials and found a small overall reduction in pain with important variation by treatment parameters.[28,29] Conversely, the 2019 American College of Rheumatology/Arthritis Foundation guideline, published in 2020, strongly recommended against TENS for knee and hip OA on the basis of the evidence available at that time.[30] These differing conclusions illustrate how sensitive the evidence base is to study selection, analytic methods, stimulation protocols, and the accumulation of newer trials. Because the present search ended on 9 March 2021, its pooled estimates represent evidence available only up to that date and should be updated before contemporary clinical recommendations are made.

This review has several limitations. First, only eight studies contributed to the primary pain meta-analysis, limiting precision and the ability to investigate small-study or publication bias. Second, substantial heterogeneity remained after exploratory subgroup analyses. Third, three of the 11 included trials were judged at high overall risk of bias and four had some concerns, which reduces confidence in

the pooled findings. Fourth, leave-one-out analysis showed that two influential studies materially affected both the pooled effect and heterogeneity.[16,19] Fifth, variable TENS protocols, outcome instruments, comparator conditions, and follow-up times limit direct clinical translation. Finally, the search date is now remote relative to the current evidence base. An updated review should rerun all databases and trial registries, reassess risk of bias and GRADE certainty, and repeat the meta-analysis using the complete contemporary evidence set.

An important interpretive issue is the distinction between the direction or magnitude of a point estimate and the certainty that the observed effect represents a true and clinically meaningful benefit. The pain estimate (Hedges g -0.53) could be described as a moderate standardized effect in magnitude, but its 95% confidence interval ranged from a potentially large benefit to a small effect in the opposite direction. Therefore, the point estimate should not be used alone to claim efficacy. In addition, an SMD is dimensionless and does not directly indicate how many points a patient might improve on a familiar pain scale. Translation into clinical relevance would require information on the underlying scales, their direction, and accepted thresholds for meaningful improvement. A similar concern applies to function: the pooled MD of -3.74 points is difficult to interpret without confirming that the WOMAC function scores were harmonized to the same range and direction across included trials. Reporting responder outcomes, absolute changes on common scales, or the proportion of participants achieving a minimally important improvement would make future trials and meta-analyses more clinically interpretable. These issues reinforce the need to describe the present estimates as suggestive rather than conclusive.

The design of TENS trials also creates specific challenges for internal validity. A credible sham should resemble active TENS sufficiently to maintain participant blinding while avoiding an active analgesic dose; however, sensory differences between active and sham stimulation can make blinding difficult. Because pain and self-reported function are susceptible to expectations and contextual effects, inadequate blinding may exaggerate treatment effects even when randomization is otherwise appropriate. Adherence, use of rescue analgesics, concurrent exercise, and therapist contact can further influence outcomes and should be measured and balanced between groups. These considerations are consistent with the RoB 2 concerns observed in several included trials.[13] Safety also requires cautious interpretation. The pooled adverse-event RR had a wide confidence interval and was based on relatively few events; it therefore cannot support a claim that TENS protects against worsening OA symptoms. Absence of a detected increase in adverse events is not equivalent to proof of safety, particularly when trials are small or adverse events are collected inconsistently. Future RCTs should prespecify adverse-event definitions, severity, relatedness, withdrawal due to adverse events, and

serious adverse events, and should report these outcomes by treatment arm using consistent denominators.

Future evidence synthesis should address both the age of the current search and the heterogeneity of the intervention. An updated review should use a prospectively registered protocol when feasible, follow PRISMA 2020 reporting, and document complete database- and registry-specific search strategies.[11,12] Eligibility criteria should prespecify whether pilot randomized trials, low-frequency protocols, combination interventions, and different pain contexts (rest, movement, or task-related pain) are eligible for quantitative pooling. Primary time points should also be defined in advance so that immediate analgesic effects are not combined indiscriminately with short- or longer-term treatment effects. If sufficient studies are available, clinically plausible subgroup analyses could examine stimulation frequency, intensity, pulse width, session duration, cumulative treatment exposure, comparator credibility, co-intervention, and OA severity; meta-regression should be used cautiously to avoid overinterpretation when the number of studies is small. The larger syntheses published after the present search suggest that the evidence base has expanded substantially and that treatment parameters may modify observed effects.[28,29] An updated GRADE assessment should then integrate risk of bias, inconsistency, indirectness, imprecision, and potential publication bias for each patient-important outcome.[14] Such an approach would allow the role of TENS to be judged against contemporary guideline-based management rather than against an evidence base ending in early 2021.[30]

Clinically, TENS may remain an optional non-pharmacological adjunct for selected patients who prefer or require additional symptom-management strategies, but the present analysis does not support presenting it as an established substitute for guideline-based core therapy. Treatment decisions should consider patient preference, contraindications, access, and response to evidence-based non-pharmacological and pharmacological management.

CONCLUSION

Among trials identified through March 2021, TENS showed a direction toward lower pain and better function in knee OA, but the pooled estimates were imprecise and did not exclude no effect. The estimate for adverse events was also uncertain. Given substantial heterogeneity, low certainty for pain and function, and sensitivity to influential studies, these findings do not support a definitive efficacy claim. Updated searches and larger, rigorously conducted sham-controlled trials with standardized TENS parameters are required before firm clinical recommendations can be made.

CONFLICT OF INTEREST

The authors declare that there are no competing interests in this study.

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