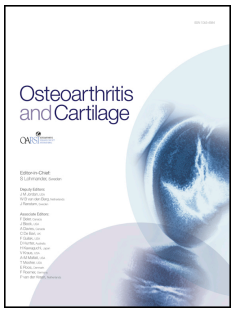

Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRELKA randomized clinical trial

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Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRELKA randomized clinical trial

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Abstract

Objective: To determine the effectiveness of TENS at relieving pain and improving physical function as compared to placebo TENS, and to determine its safety, in patients with knee osteoarthritis.

Methods: Multi-centre, parallel, 1:1 randomized, double-blind, placebo-controlled clinical trial conducted in 6 outpatient clinics in Switzerland. We included 220 participants with knee osteoarthritis recruited between October 15, 2012, and October 15, 2014. Patients were randomized to 3 weeks of treatment with TENS (n=108) or placebo TENS (n=112). Our pre-specified primary endpoint was knee pain at the end of 3-weeks treatment assessed with the WOMAC pain subscale. Secondary outcome measures included WOMAC physical function subscale and safety outcomes.

Results: There was no difference between TENS and placebo TENS in WOMAC pain at the end of treatment (mean difference -0.06; 95%CI -0.41 to 0.29; p=0.74), nor throughout the trial duration (p=0.98). Subgroup analyses did not indicate an interaction between patient/treatment characteristics and treatment effect on WOMAC pain at the end of treatment (p-interaction ≥0.22). The occurrence of adverse events was similar across groups, with 10.4% and 10.6% of patients reporting events in the TENS and placebo TENS groups, respectively (p=0.95). No relevant differences were observed in secondary outcomes.

Conclusions: TENS does not improve knee osteoarthritis pain when compared to placebo TENS. Therapists should consider other potentially more effective treatment modalities to decrease knee osteoarthritis pain and facilitate strengthening and aerobic exercise. Our findings are conclusive and further trials comparing TENS and placebo TENS in this patient population are not necessary.

Keywords: Osteoarthritis, TENS, pain, randomized clinical trial

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disease and one of the leading causes of disability in adults worldwide.[1] OA is associated with decreased quality of life and frequent use of the health care system.[2] Currently, no treatment can stop or reverse the progressive joint degeneration caused by OA. Most clinical interventions aim to improve pain and disability as these are the main symptoms afflicting OA patients.[3]

Transcutaneous electric nerve stimulation (TENS) is widely used in the management of knee OA to relieve osteoarthritic pain and facilitate the performance of therapeutic activities in order to maintain or improve physical function.[4] A systematic review of guidelines for the management of knee and hip OA reported that 8 out of 10 guidelines recommend the use of TENS.[5] TENS is based on the 'Gate-Control Theory' of pain perception as described by Melzack and Wall.[6] This theory suggests that afferent stimulation, such as electrical stimulation, competes with painful stimulation in the spinal cord level, which attenuates the perception of pain at the central nervous system. Another suggested mechanism includes the stimulation of β-endorphin production.[7, 8] It has been suggested that TENS can improve the clinical course of knee OA, with fewer adverse effects than medical treatment.[9, 10]

In a Cochrane review, we found that the evidence suggesting a beneficial treatment effect of TENS for knee OA pain was based only on small trials of questionable quality with imprecise estimates of effect.[9, 11] Notwithstanding the low quality of the currently available evidence, with large uncertainty about the magnitude of its effect,[11] the findings of the review indicated that TENS has a potentially clinically relevant effect on knee pain and physical function and warranted further evaluation with a properly designed clinical trial. Therefore, we conducted an adequately powered, high-quality randomized controlled trial (RCT) to determine the effectiveness of TENS at relieving pain and improving physical function compared to placebo TENS, and to determine its safety, in patients with primary or post-traumatic knee OA.

METHODS

Trial design and patients

This was a multi-centre, parallel, randomized, double-blind (patient and assessor), placebo-controlled clinical trial, which randomized patients to TENS or Placebo TENS treatment.

Patients were recruited in six outpatient clinics in Switzerland. We enrolled men and non-pregnant women, at least 18 years of age, with symptomatic, radiologically confirmed knee OA according to the criteria of the American College of Rheumatology,[12] with knee pain lasting for six months or longer, and radiographic evidence of at least one osteophyte at the tibiofemoral joint (Kellgren-Lawrence grade ≥ 2).[13] See Web-appendix 1 for the full list of eligibility criteria. The index knee was defined as the most painful knee as identified by the patient. All patients provided written informed consent. The trial complied with the principles of the Declaration of Helsinki, was approved by the independent research ethics committee of Canton Bern, and registered before trial initiation at ClinicalTrials.gov (NCT01875042).

Randomization and interventions

Patients were randomly assigned on a 1:1 basis to the TENS or placebo TENS group. The computer-generated random sequence of allocation was concealed using a web-based system for central randomization. Randomization was stratified by treatment centre, clinical severity (≤4 versus >4 on a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[14] standardized to range from 0 to 10), and by whether patients had previously received TENS with randomly varied block sizes of 2, 4, and 6. Patients were randomized by the recruiting physician once demographic data was collected, radiographs done, and eligibility criteria confirmed.

TENS and placebo TENS treatment sessions were conducted 4 times in the first week, 3 times in the second week, and 2 times in the third week. Each session lasted up to 60 min, depending on symptom presentation. Sessions were conducted at treatment centres and interventions were delivered by trained unblinded study personnel following a standardized protocol. Prior to the first treatment session, patients were instructed to completely remove all body hair from the knee receiving the intervention. Before each application, the area where electrodes were positioned were cleaned with alcohol to improve skin conductivity. Patients assumed a supine position and rested

their legs over a pillow with approximately 15° of knee flexion. Two electrodes with sponge inserts of the same dimension were secured by straps over the medial and lateral aspects of the index knee, perpendicular to the length of the limb and over the joint line. The therapist set the TENS stimulation parameters and intensity according to the patient allocation to active or placebo intervention. In the experimental group, the TENS modality was individualized using typically recommended stimulation parameters (low-frequency, high-frequency, or burst TENS), according to symptom presentation (Web-appendix 2, Web-appendix Tables 1 and 2). In the control group, we applied the identical stimulation approach as in the experimental group as described in Web-appendix Tables 1 and 2 using the same devices. However, to achieve a credible placebo TENS, we used a specific device setting that allowed to deliver the currents for 45 seconds after the stimulation parameters had been set, and then automatically slowly ramped down until it was off.[15] Instead of the question whether the patients felt the stimulation (as was asked to patients receiving the active treatment to increase the intensity of stimulation, if needed), the participants in the placebo group were asked whether they felt well, every 5 minutes (placebo burst or low-frequency TENS) or 10 minutes (placebo high-frequency TENS). To maintain blinding of the participants, they were kept unaware of the study design and the use of placebo TENS. Participants were informed in a neutral manner that 2 different types of TENS were being compared. The physiotherapists and study nurses who coordinated the clinical visits could not be blinded to treatment group but were asked not to disclose the treatment or the nature of the control TENS component to participants. The trial was considered to entail no more than minimal risk and burden to participants. Therefore, the responsible research ethics committee did not classify the trial as involving incomplete participant information. We debriefed participants after the trial was completed nonetheless.

Outcomes

The pre-specified primary endpoint was overall knee pain intensity at the end of treatment at 3-weeks follow-up, as assessed by the WOMAC pain subscale (Likert version ranging from 0 to 20).[16] Secondary outcomes were overall knee pain measured on a visual analogue scale (VAS); WOMAC global score, physical function and stiffness subscales; hospital anxiety and depression scale;[17] Aberdeen measure of participation;[18] proportion of patients responding to treatment, defined as 30% or 50%

decreases in baseline WOMAC pain scores;[19] mean analgesic intake per patient; numbers of patients experiencing local adverse events, any adverse event, serious adverse events (defined as events resulting in hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events or death); overall number of patients that dropped out; and, the number of patients that dropped out due to adverse events. Success of blinding of patients was assessed using a modified blinding index originally described by James et al,[20] which ranges from 0 to 1, where 0 denotes complete failure of blinding and 1 indicates complete success of blinding.[21] All continuous effectiveness outcomes were standardized to range from 0 to 10, with higher scores indicating a higher disease severity. Standardized minimally important clinical difference estimates are provided to facilitate the interpretation of the treatment effect reported on a standardized scale from 0 to 10. Not all of the secondary outcomes have established minimally important clinical differences. Thus, we used a distribution based approach[22] to derive the following minimally important clinical difference for secondary outcomes on a 0-10 scale: WOMAC function: 1.0; WOMAC stiffness: 1.1; WOMAC global score: 0.9; VAS overall: 1.0; hospital anxiety score: 0.7; hospital depression score: 0.4; Aberdeen measure of participation: 0.5. The minimal important clinically difference for WOMAC pain, the primary outcome, is 1.0 as explained in the statistical analysis section. WOMAC pain was assessed at baseline, at 1-week follow-up (i.e., after 4 treatment sessions), at the end of treatment at 3-weeks follow-up, and at 3-months follow-up. All other effectiveness outcomes were assessed at baseline, at the end of treatment, and at 3-months follow-up. Safety outcomes were recorded at each visit and at 3 months follow-up. Baseline and end-of-treatment outcomes were ascertained by study personnel unrelated to the care of randomized patients and 3-month data were collected using patient-administered postal questionnaires and telephone interviews by outcome assessors blinded to treatment allocation, if needed. All patients and study personnel recording outcome data were blinded as to the allocated intervention.

Statistical analysis

A sample size of 100 patients per group yielded 80% power to detect a clinically relevant difference of 1.0 on the WOMAC pain subscale standardized to range from 0 to 10 with a typical standard deviation of 2.5, at a two-sided alpha level of 0.05 using a t-test to analyse WOMAC pain scores at 3-weeks follow-up. This difference

corresponds to a clinically meaningful moderate effect size of 0.4.[23] The protocol pre-specified the use of analysis of covariance for all continuous outcomes, adjusted for the outcomes' baseline values. For this approach, a sample size of 99 patients would yield 90% power, assuming a correlation of 0.5 between baseline and 3-week follow-up. As we anticipated an up to 10% attrition rate, we recruited a total of 220 patients.

At each time-point, continuous outcomes were analysed using analysis of covariance adjusted for the outcome's baseline values, and binary outcomes were analysed using chi-squared tests. A repeated-measures analysis was conducted to assess the overall between-group difference in WOMAC pain across all time-points. Analyses were based on the intention-to-treat principle, whereby all randomized patients were included in the analysis according to their allocated group.[24] We used multiple imputation to impute missing outcome data. All P values and 95% confidence intervals (CIs) were two-sided. All analyses were conducted in Stata 13.0, and in R and the ReporteRs package (R core team 2016) by an independent statistician of an academic clinical trials unit (CTU Bern, Switzerland) who was unaware of the group assignments. In addition, the data were interpreted and conclusions formulated prior to investigators being unblinded to treatment allocation. See Web-appendix 3 for description of subgroup and sensitivity analyses and multiple imputation methods.

RESULTS

Characteristics of patients and treatment

Between October 15, 2012 and October 15, 2014, a total of 220 patients were enrolled, with 108 patients randomly allocated to the TENS group and 112 to the placebo TENS group, who were all included in the intention-to-treat analyses (Figure 1). Table 1 displays the baseline characteristics of randomized patients, which were similar across groups. Patients in the TENS and placebo TENS groups were on average 65 and 66 years old, proportions of females was 48% and 54%, respectively, and 68 (63%) and 57 (51%) of patients had the right knee classified as the index knee. Web-appendix Tables 3-5 display the characteristics of the interventions received in each group. Burst TENS was most commonly used in the first treatment session (97% and 98% of patients in the TENS and placebo TENS group, respectively), and throughout the full course of treatment (99% in both treatment groups). A blinding index of 0.94 (one-sided lower 95% CI 0.91) indicated that blinding of patients was successful. Among naïve participants, 7 (7.4%) out of 94 in the TENS group, and 3 (3.1%) out of 96 in the placebo TENS group, were able

to guess the treatment they received. Among non-naïve participants, 0 (0%) out of 13 in the TENS group, and 3 (20.0%) out of 15 in the placebo TENS group, were able to guess the treatment they received.

Effectiveness outcomes

As shown in Table 2, there was no difference between TENS and placebo TENS in WOMAC pain at the end of treatment, our pre-specified primary outcome (mean difference -0.06; 95% CI -0.41 to 0.29; p=0.74). Figure 2 displays the effect of treatment on WOMAC pain for each group across all time-points, with no difference between groups throughout (p=0.98). Both groups had a clinically significant reduction of at least 1 point in the WOMAC pain on a 0-10 scale at the end of treatment (p<0.001). The reduction in pain persisted for both groups at 3 months after the end of treatment (p<0.001), albeit below the threshold of clinical relevance. Figure 3 displays the analysis of the primary outcome, WOMAC pain at the end of treatment, according to different patient and treatment characteristics. None of these characteristics seemed to interact with the treatment effect (p for interaction ≥0.22). Web-appendix Table 6 displays results of sensitivity analyses based on per-protocol and complete-cases datasets, which also indicated no difference between groups for WOMAC pain (p≥0.78) (Web-appendix Table 6). Sensitivity analyses with univariate and multivariable models adjusting for different treatment characteristics also indicated no evidence of a difference between groups for WOMAC pain (p≥0.73) (Web-appendix Table 7).

Table 2 displays the between group difference for all effectiveness continuous outcomes, at the end of treatment and at 3 months follow-up, with no significant differences between groups. Table 3 displays the proportion of patients that reported 30% and 50% reductions in WOMAC pain from baseline to end of treatment, and corresponding numbers-needed-to-treat, again with no significant difference between groups for a 30% reduction in WOMAC pain (risk difference 0.11; 95% CI -0.02 to 0.24; p=0.090), nor for a 50% reduction (p=0.66). There were no significant differences between groups regarding analgesic consumption (mean difference 0.01; 95% CI -0.02 to 0.03; p=0.65), with a median consumption of 0mg (IQR 0 to 2500) in the TENS group and 0mg (IQR 0 to 1750) in the placebo group.

Safety outcomes

None of the patients experienced serious adverse events. However, three patients discontinued their therapy because they experienced adverse events. One (0.94%) of the patients received TENS and the other two (1.77%) received placebo (odds ratio 1.89; 95% CI 0.17 to 21.17; p = 0.60). All adverse events were minor and common transient local skin reactions related to TENS treatment that did not require medical attention. The occurrence of adverse events was similar across groups, with 10.4% and 10.6% of patients reporting events in the TENS and placebo TENS groups, respectively (odds ratio 1.03; 95% CI 0.43 to 2.44; p = 0.95).

DISCUSSION

Statement of principal findings

In this randomised controlled trial in 220 patients with knee OA we did not find a difference between TENS and placebo on WOMAC pain at the end of treatment. The confidence intervals of the mean difference in WOMAC pain of -0.06 (95% CI -0.41 to 0.29) at the end of treatment rule out any clinically relevant benefit of TENS. A similar null effect was observed during treatment and at 3 months after the end of treatment, as well as for all other patient relevant secondary outcomes assessed, namely physical function, joint stiffness, global disease severity, and emotional status. In subgroup analyses of the primary outcome by age, gender, pain severity at baseline, radiographic disease severity at baseline, and TENS naivety, we did not identify any subgroup of patients that could potentially benefit from TENS. Our findings thus suggest that any effect of TENS on knee OA observed in a clinical setting is due to placebo effects and/or natural history of OA.

Strengths and weaknesses of the study, and in relation to other studies

This is the first adequately powered trial with adequate methods of randomization, concealment of allocation, and blinding of patients and a low risk of incomplete outcome data bias. The overall drop-out rate was only 2.7% and nondifferential across groups (2.8% in the TENS and 2.7% in the placebo TENS group). Missing data were properly accounted for using multiple imputation. Given the intricate nature of the interventions, treatment was delivered by therapists to ensure treatment quality and adherence to the protocol. It has also been suggested that TENS should be used for as long as desired to help cope with chronic pain, which was not possible in the present trial since interventions were delivered in a clinical setting. However, recent evidence indicates that there is also no difference between TENS and placebo TENS even with prolonged treatment during daily activities.[25] We used methods to minimize the risk of biases in our results where possible. It is common for subjects to adapt to TENS current in a way that they no longer feel the stimulation over time, or that the stimulation is felt at a lower intensity. Our approach to placebo TENS aimed to mimic active TENS and was more likely to lead to successful blinding compared to prior trials that used placebo devices that appeared to be functioning but had broken leads so that no current was delivered at any time.

It has been previously shown that the placebo TENS used in our trial successfully mimics a real TENS treatment without generating a treatment effect on pain.[15] In addition, once the current was off, our placebo device still indicated on the digital display that the current was on. We included patients regardless of previous TENS treatment experience, for a broader generalizability of our results. Although the inclusion of patients with previous TENS experience could have partially compromised patient blinding in our trial, a subgroup analysis according to TENS naivety indicated that there was no difference in treatment effects between patients with and without previous TENS experience. In fact, a blinding index of 0.94 indicated that blinding of patients was successful. Nonetheless, it was not possible to blind the treating therapists, as they had to set the TENS equipment to deliver real or placebo treatment. The lack of blinded therapists could have led to performance bias if, for instance, unblinded therapists provided co-interventions to patients receiving placebo treatment. We explicitly defined in our protocol that therapists should not provide co-interventions in addition to the experimental treatments. The mean baseline WOMAC pain score of patients included in this trial was approximately 3.5 on a 0-10 scale. Although the knee OA pain experienced by patients was significant enough to seek medical care, an average score of 3.5 indicates only mild pain. This may limit the generalizability of our results to patients with a similar pain score. However, a subgroup analysis according to baseline WOMAC pain score (i.e. ≤4 or >4 on a 0-10 scale) indicated that the effect of TENS did not change according to the severity of pain at baseline (p for interaction = 0.57). Nevertheless, our results are not generalizable to patients with severe pain as they were underrepresented in the current trial. Although several different TENS modalities can be used to treat knee OA, we only used low-frequency, high-frequency, or burst TENS as TENS modalities in the current trial. This decision was based on our systematic review, which identified low-frequency, high-frequency, or burst TENS as the TENS modalities with higher probability of treatment success.[11] Finally, in most centres, the trial interventions were delivered by physical therapists. In one of the centres, interventions were delivered by study nurses. None of the study nurses had previous experience with treating patients with TENS. Having said that, all therapists in this trial were trained to standardize the delivery of interventions according to protocol, and the treatment effects were homogenous across the six outpatient clinics that participated in this trial.

Meaning of the study

In a Cochrane review on TENS for knee OA, we reported that the evidence was inconclusive since only small trials of questionable quality were identified.[11] However, we also noted some indication that TENS may improve the symptoms of patients with knee OA. The reported overall effect of TENS was a standardized mean difference of -0.86 (95% CI -1.23 to -0.49), which corresponded to a between-group difference of -2.15 (95% CI -3.08 to -1.23), as measured on a 10-point WOMAC pain subscale. This effect estimate was over 2 times what patients report as a minimally clinically relevant effect,[26] a similar effect expected with total joint replacement. We recommended that a properly powered trial using adequate methods to minimize the risks of bias was needed to provide a definite answer regarding the effectiveness of TENS. In addition, we predicted the effect on pain intensity in trials as large as the largest included trial in the review, resulting in an estimate of -0.07 (95% CI -0.46 to 0.32), which is near identical to the estimates we observed in our current trial. Several trials comparing TENS with placebo TENS have been published since 2009.[27-38] As in the preceding trials, the number of participants randomized per trial arm were low (range 10 to 74), whereas the risk of bias was deemed to be high in all but one study.[35] We could derive effect sizes for the majority of studies for the outcome pain relief, which varied from close to zero to -0.72 standard deviation units difference, with the larger trials suggesting no benefits of TENS.[28, 33, 35]

Current clinical practice guidelines either make no recommendation for the use of TENS in knee OA treatment or recommend against its use, which aligns with the low quality of the available evidence. The American College of Rheumatology strongly recommended against the use of TENS, arguing that only small trials of limited methodological quality are available.[39] The guidelines of the American Academy of Orthopaedic Surgeons stated that the evidence is inconclusive, and provided no recommendations for or against the use of TENS.[40] Likewise, the Osteoarthritis Research Society International (OARSI) considered the evidence on the use of TENS in knee OA as “uncertain”, and also did not provide any recommendations for its use.[41] The most recent version of the OARSI guidelines did not make any recommendation about TENS.[42]

Unanswered questions and future research

This is the first adequately powered randomized trial that compared TENS and placebo TENS in a sufficient number of patients to detect a minimal clinically relevant difference between groups. Between-group differences in knee pain across all time-points were near null, and the 95% confidence intervals during and at end of treatment and at 3 months follow-up excluded any potentially clinically relevant effect, since their lower bounds did not reach the minimal clinically important difference of -1. Results for all pre-specified primary and secondary outcomes indicated a null between-group difference, and 95% confidence intervals generally excluded a clinically relevant benefit. The settings used for TENS in our trial are commonly used in current clinical practice. We therefore consider our findings conclusive and believe that further trials comparing TENS and placebo TENS in this patient population are not necessary. To optimize care and minimize costs, therapists should consider other potentially more effective treatment modalities to decrease knee OA pain and facilitate strengthening and aerobic exercise when treating patients with symptomatic knee OA.[43]

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Contributorship: Drs. Reichenbach and da Costa had full access to all of the data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: Rutjes, da Costa, Jüni, Lucas, Reichenbach. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: da Costa, Jüni, Hincapié, Reichenbach. Critical revision of the manuscript for important intellectual content: All authors. Statistical expertise: da Costa, Jüni, Schürch. Administrative, technical, or logistic support: Lucas, Reichenbach, Rutjes. Obtaining of funding: da Costa, Juni, Reichenbach, Rutjes.

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Data sharing statement: The guarantors are willing to examine all requests for the full dataset after a period of three years from the date of this publication. Participants did not give consent for data sharing but the data are anonymized and risk of identification is low.

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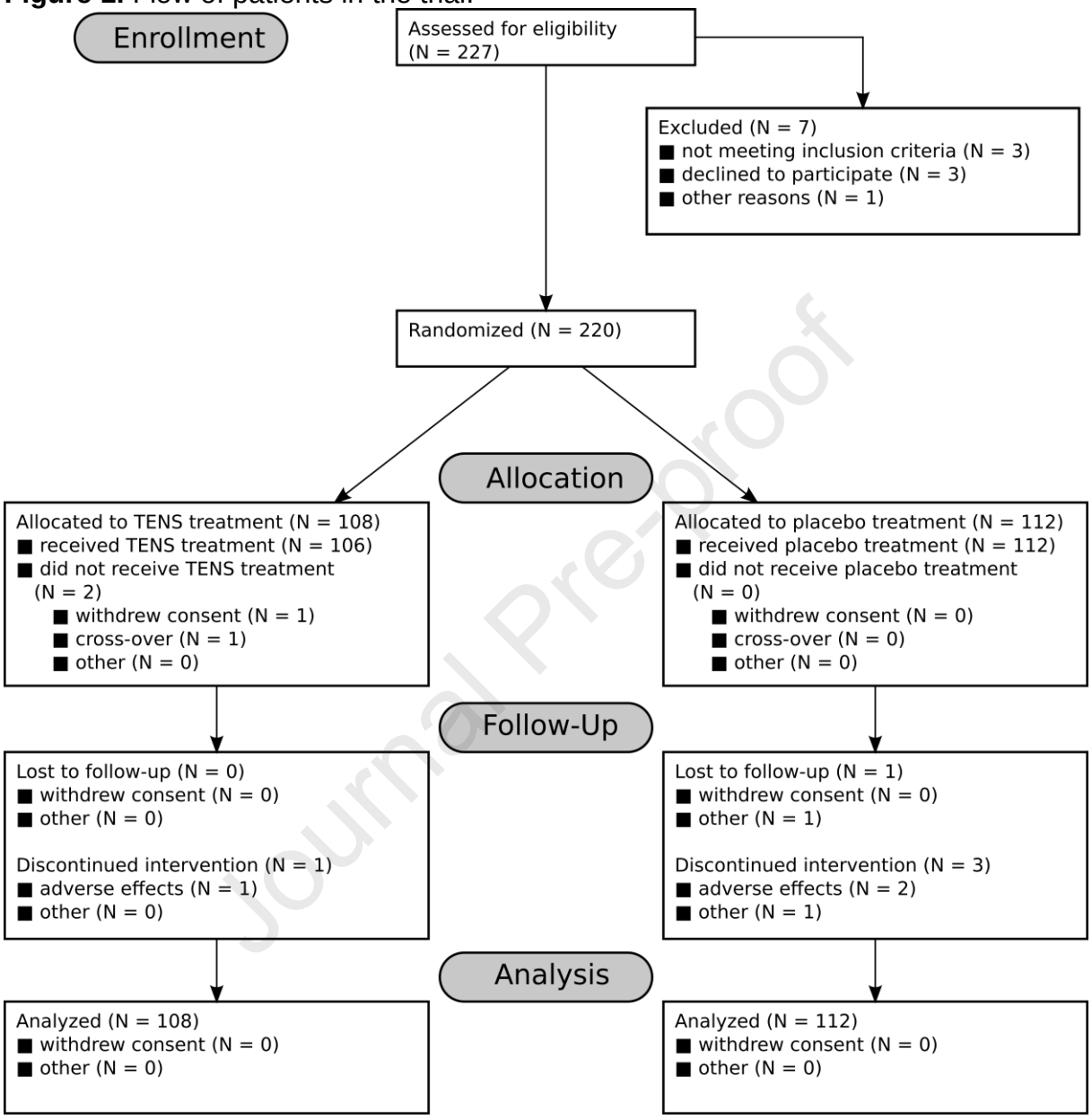
DISPLAY ITEMS

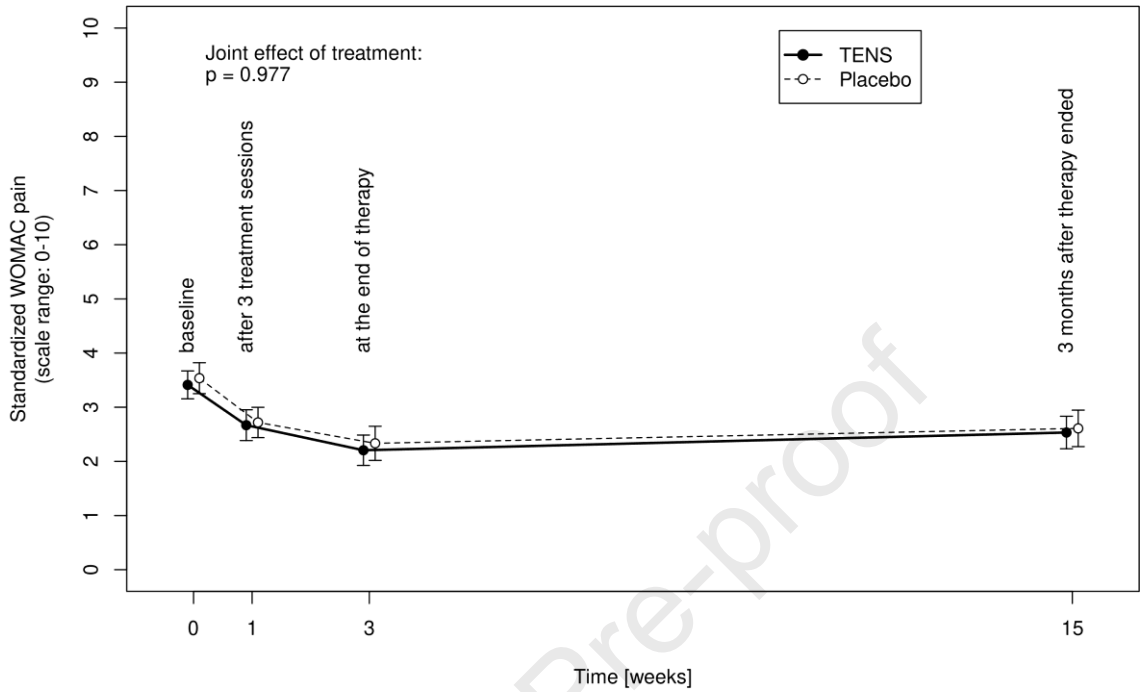
FIGURES

Figure 1. Flow of patients in the trial.



One participant randomly allocated to receive TENS treatment, received placebo TENS by mistake for all treatment sessions.
Numbers shown for Follow-up and Analysis concern our primary outcome WOMAC pain at the end of treatment. At 3 months follow-up, there were 0 and 2 participants lost to follow-up, and 108 and 112 participants included in the analysis, for TENS and placebo treatment, respectively.

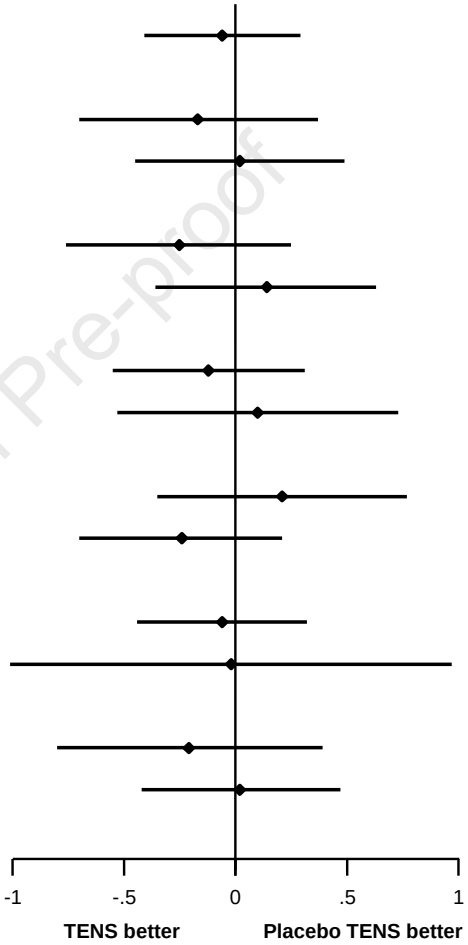
576 **Figure 2.** Group-specific treatment effects on WOMAC pain across time points. Data displayed are
577 means and 95% confidence intervals.



578
579
580 WOMAC pain values are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity.

581 **Figure 3.** Subgroup analyses of the primary outcome of WOMAC pain according to different patient and treatment characteristics.

	TENS		Placebo TENS			
	n	Mean ± SD	n	Mean ± SD	Difference in means (95% CI)	P-value
Overall	108	2.20 ± 1.48	112	2.34 ± 1.69	-0.06 (-0.41 to 0.29)	
Age						0.61
<65	48	2.28 ± 1.54	48	2.48 ± 1.79	-0.17 (-0.70 to 0.37)	
≥65	60	2.14 ± 1.44	64	2.23 ± 1.62	0.02 (-0.45 to 0.49)	
Gender						0.28
males	56	2.02 ± 1.22	52	2.36 ± 1.62	-0.25 (-0.76 to 0.25)	
females	52	2.40 ± 1.22	60	2.32 ± 1.62	0.14 (-0.36 to 0.63)	
WOMAC pain at baseline						0.57
≤4	74	1.78 ± 1.18	76	1.91 ± 1.36	-0.12 (-0.55 to 0.31)	
>4	34	3.12 ± 1.66	36	3.24 ± 1.96	0.10 (-0.53 to 0.73)	
Kellgren-Lawrence grade						0.22
<3	42	2.11 ± 1.36	45	1.93 ± 1.60	0.21 (-0.35 to 0.77)	
3-4	66	2.26 ± 1.55	67	2.61 ± 1.71	-0.24 (-0.70 to 0.21)	
TENS naïvety						0.94
naïve	95	2.14 ± 1.49	97	2.25 ± 1.60	-0.06 (-0.44 to 0.32)	
experienced	13	2.65 ± 1.33	15	2.87 ± 2.21	-0.02 (-1.01 to 0.97)	
Volume of centers						0.54
low (<40 patients)	40	2.12 ± 1.41	39	2.43 ± 1.45	-0.21 (-0.80 to 0.39)	
high (≥40 patients)	68	2.25 ± 1.53	73	2.29 ± 1.81	0.02 (-0.42 to 0.47)	



582
583 CI: confidence interval; WOMAC: Western Ontario and McMaster Universities Arthritis Index. Difference in means and p-values are adjusted for the baseline value of WOMAC pain. WOMAC pain values
584 are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity. Pre-specified subgroup analyses of the primary outcome: WOMAC pain at baseline (≤4 vs >4),
585 TENS naivety, and the study center's number of included patients (<40 patients vs ≥40 patients). The remaining subgroup analyses were specified after completion of the statistical analysis plan, but
586 before inspection of the data, and were considered post hoc: age (<65 vs ≥65), gender, Kellgren-Lawrence grade of osteoarthritis (<3 vs 3-4).

TABLES

Table 1. Characteristics of patients included at baseline.

	TENS N = 108	**Placebo TENS** N = 112
Age (years), mean±SD	64.8 ± 9.9	66.3 ± 10.3
Female, N(%)	52 (48%)	60 (54%)
BMI, mean±SD	27.5 ± 4.9	26.9 ± 4.9
WOMAC pain, mean±SD	3.4 ± 1.4	3.5 ± 1.5
Clinical Severity, N(%)		
non-severe (WOMAC pain ≤4)	74 (69%)	76 (68%)
severe (WOMAC pain >4)	34 (31%)	36 (32%)
WOMAC function, mean±SD	3.4 ± 1.6	3.5 ± 1.8
WOMAC stiffness, mean±SD	3.8 ± 2.0	4.0 ± 2.2
WOMAC global score, mean±SD	3.4 ± 1.4	3.6 ± 1.6
VAS pain overall , mean±SD	4.1 ± 1.7	4.1 ± 2.1
Hospital anxiety score, mean±SD	3.0 ± 1.3	3.0 ± 1.5
Hospital depression score, mean±SD	6.1 ± 0.7	6.1 ± 0.7
Aberdeen measure of participation, mean±SD	2.5 ± 1.0	2.5 ± 1.0
Daily paracetamol equivalence dose in mg, median (IQR)	1750 (0 to 5250)	955 (0 to 5000)
Body side of the treated knee, N(%)		
left	40 (37%)	55 (49%)
right	68 (63%)	57 (51%)
Crepitus in the treated knee, N(%)	69 (64%)	70 (63%)
Kellgren-Lawrence grade, N(%)		
2	42 (39%)	45 (40%)
3	43 (40%)	42 (38%)
4	23 (21%)	25 (22%)

SD: standard deviation; BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual analogue scale; IQR: Interquartile range. All outcomes are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity.

Table 2. Treatment effects at the end of treatment (3 weeks), and at specified time points, from intention to treat analysis. All values are means and standard deviation unless otherwise specified.

Outcome	TENS (N = 108)	Placebo TENS (N = 112)	Difference in means (95% CI)	p-value
WOMAC pain				
week 1	2.67 ± 1.50	2.72 ± 1.51	0.03 (-0.26 to 0.33)	0.82
week 3	2.20 ± 1.48	2.34 ± 1.69	-0.06 (-0.41 to 0.29)	0.74
week 15	2.53 ± 1.59	2.60 ± 1.80	0.01 (-0.37 to 0.39)	0.98
WOMAC function				
week 3	2.51 ± 1.61	2.58 ± 1.85	0.02 (-0.32 to 0.35)	0.93
week 15	2.74 ± 1.71	2.75 ± 1.96	0.08 (-0.28 to 0.43)	0.66
WOMAC stiffness				
week 3	3.04 ± 2.07	2.85 ± 2.04	0.30 (-0.17 to 0.77)	0.21
week 15	3.20 ± 2.01	2.97 ± 2.23	0.35 (-0.14 to 0.83)	0.16
WOMAC global score				
week 3	2.49 ± 1.53	2.55 ± 1.74	0.03 (-0.29 to 0.35)	0.85
week 15	2.74 ± 1.62	2.74 ± 1.86	0.10 (-0.24 to 0.44)	0.57
VAS overall				
week 3	2.54 ± 1.86	2.51 ± 1.88	0.02 (-0.40 to 0.44)	0.91
week 15	3.03 ± 2.09	2.93 ± 2.26	0.09 (-0.41 to 0.59)	0.71
Hospital anxiety score				
week 3	2.87 ± 1.21	2.77 ± 1.39	0.11 (-0.15 to 0.36)	0.41
week 15	2.75 ± 1.30	2.82 ± 1.39	-0.06 (-0.31 to 0.18)	0.61
Hospital depression score				
week 3	5.99 ± 0.64	6.05 ± 0.69	-0.05 (-0.21 to 0.10)	0.50
week 15	6.04 ± 0.63	5.97 ± 0.80	0.07 (-0.11 to 0.25)	0.46
Aberdeen measure of participation				
week 3	2.55 ± 0.98	2.38 ± 0.91	0.19 (-0.01 to 0.39)	0.067
week 15	2.42 ± 0.84	2.45 ± 0.97	-0.02 (-0.23 to 0.20)	0.89

CI: confidence interval; WOMAC: Western Ontario and McMaster Universities Arthritis Index. Difference in means and p-values are adjusted for the baseline value of the respective outcome. All outcomes are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity.

599 **Table 3.** Proportion of patients that reported 30% and 50% reduction in WOMAC pain from baseline to
600 end of treatment.
601

Outcome	TENS (N = 108)	Placebo (N = 112)	Risk difference (95% CI)	p-value	NNT/NNH (95% CI)
50% responders	38%	41%	-0.03 (-0.16 to 0.10)	0.66	NNH -34.31 (NNT 9.93 to NNH -6.29)
30% responders	62%	50%	0.11 (-0.02 to 0.24)	0.090	NNT 8.81 (NNT 4.09 to NNH -57.05)

602 CI: confidence interval, NNT: numbers needed to treat; NNH numbers needed to harm
603
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Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRELKA randomized clinical trial

WEB-APPENDIX

Table of Contents

Transcutaneous electrical nerve stimulation (TENS) in patients with symptomatic knee osteoarthritis: a randomized controlled trial

Web-appendix 1. Detailed eligibility criteria

Participants fulfilling all of the following **inclusion criteria** are eligible for the trial:

1. Men and non-pregnant women
2. At least 18 years of age
3. Symptomatic, radiologically confirmed knee OA according to the criteria of the American College of Rheumatology
4. Knee pain lasting for six months or longer
5. Radiographic evidence of at least one osteophyte at the tibiofemoral joint (Kellgren-Lawrence grade ≥ 2).
6. One or more of the following signs and symptoms in the knee:
    a. restricted range of motion
    b. pain with motion
    c. crepitation
    d. morning stiffness.

The presence of any one of the following **exclusion criteria** led to exclusion of the participant:

1. Diagnosed with rheumatoid arthritis or other musculoskeletal diseases affecting lower extremities
2. Relevant effusion in the index knee (defined as the most painful knee as identified by the patient)
3. Known current or remittent cancer
4. Had a cardiac pacemaker or defibrillator in situ
5. Had knee surgery in previous 6 months
6. Received treatment with arthrocentesis
7. Received intra-articular injection of steroids during the previous 3 months
8. Unable to understand instructions.

Web-appendix 2. Description of implementation of treatment parameters

In the application of high frequency low intensity TENS (referred to as High TENS), the therapist initially fixed the frequency at 100 Hz, applying the shortest pulse duration at which the patient became aware of stimulation. Intensity was then increased to 3 times the sensory threshold, the threshold at which the patient first became aware of stimulation. At this intensity, the therapist gradually increased the pulse duration. If increasing the pulse duration lead to a broader or deeper sensation of TENS, this parameter combination was kept, otherwise the pulse duration was shortened to the most comfortable one, as indicated by the patient. If this approach was not well tolerated by the patient, an alternative approach was used, where the longest pulse duration of 400 µsec was chosen and the intensity was gradually increased to just above the sensory threshold. If the stimulation was perceived as uncomfortable, the pulse duration was shortened until the stimulation became comfortable. Intensity was then increased as described above. In the application of low frequency high intensity TENS (referred to as Low TENS), the frequency was initially set at 2 to 3 Hz and the pulse duration was gradually increased from 250 µsec to 400 µsec. Hereafter the intensity was increased to a maximum, striving at about 6 times the sensory threshold and above the motor threshold, where muscle contractions become visible. If the patient did not tolerate such high intensity, the therapist then tried using high intensity burst TENS. In the application of burst TENS, the frequency was set at 80 to 100 Hz, with a repetition frequency of 2 to 3 Hz. Intensity was then gradually increased, analogue to the Low TENS application. Although in low TENS and burst TENS the intensity optimally should be experienced as a strong, heavy or tense sensation accompanied with mild but tolerable pain, the stimulation should not lead to frank pain. The duration of stimulation was 30 minutes in all initial sessions. For low and Burst TENS, the patients were asked every 5 minutes whether they still felt the sensation, for high TENS every 10 minutes. If the patient adapted to the experimental stimulation, the intensity was gradually increased to obtain the initial sensation. If response was indicated to be minimal, at the next session stimulation parameters were altered slightly, and for high TENS the session duration was prolonged to maximally 60 minutes.

Web-appendix 3. Additional statistical analysis methods

Missing outcome data were imputed separately for each outcome using gender, age, body mass index (BMI), all WOMAC component baseline scores (pain, stiffness, physical function), analgesic intake regime (in paracetamol equivalence doses), characteristics of the treated knee, and treatment indicator as predictors in the imputation model used to generate 20 imputed datasets.[21]

We conducted pre-specified subgroup analyses of the primary outcome with accompanying tests of interaction according to WOMAC pain at baseline (≤4 vs >4), previous experience with TENS, and the study center's number of included patients (<40 patients vs ≥40 patients). The remaining subgroup analyses were specified after completion of the statistical analysis plan, but before inspection of the data and were therefore considered post hoc: age (<65 vs ≥65), gender, Kellgren-Lawrence grade of osteoarthritis (<3 vs ≥3).

We conducted sensitivity analyses based on a complete cases dataset, where only patients with complete outcome data were included, and on an as treated dataset, where all patients who attended all nine treatment sessions were included and analyzed according to the treatment received using the imputed outcomes. We also conducted sensitivity analyses to estimate the treatment effect adjusted for the following treatment characteristics: number of actual treatment sessions received; paracetamol equivalence dose of analgesic co-interventions; use of chondroitin or glucosamine; use of any food supplement; use of nonsteroidal anti-inflammatory drugs (NSAIDs); use of corticosteroids; and physiotherapy treatment other than TENS. Analgesics consumption in paracetamol equivalence dose at the end of treatment was reported as median and interquartile range (IQR) for each group and compared between groups using Wilcoxon rank-sum test for unpaired data.

Web-appendix 4. List of collaborators (therapists)

CI, CTU Bern: Ursina Sager Huber; Regula Jaeggi; Regula Dänzer; Renata Bünter

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Spital Frutigen, Frutigen: Urs Bigler; Annelies Etter

Gygax & Zurbuchen GmbH, Bern: Martin Zurbuchen; Hubert Gygax; Christa Wenker; Michelle Diener; Myriam Lang; Simone Parli; Franziska Wiedmer; Lili Barits; Barbara Guggisberg

Huttwil: Liesbeth Spiering

Physiotherapie Effingerstrasse, Bern: Sven Witjes; Rob van den Boezem; Daniel Ferrazzi; Silvan Zindel; Nicolai Loboda; Eva Kaltenbacher

Web-appendix Table 1. Case definition with stimulation parameters for the ETRELKA trial

Pain actuality	**Typical description Type/Location**	**Suggested TENS type and stimulation duration**
High: acute pain	Sharp, piercing, burning / well defined, patient can indicate pain location with his or her finger	High, 45 to 60 minutes
Intermediate: subacute pain	Any pain description falling between the acute and chronic description / reasonably defined, patient can indicate small pain area	Burst or Low, 15 to 20 minutes
Low: chronic pain	Dull, heavy, pounding, nagging / diffuse, patient uses the hand to indicate pain area	Burst or Low, 15 to 20 minutes

Web-appendix Table 2. Recommended stimulation parameters

TENS type	Puls duration	Stimulation Frequency	Intensity	Duration of session
High	10 - 75µs	50 - 200 Hz	Just above the sensory threshold up to clearly perceptible, about 3 times the sensory threshold*	30 minutes up to several hours
Low	100 - 400µs	2 - 7 Hz	Limit of tolerance, motor threshold†, 3 to 6 times the sensory threshold*	20 to 45 minutes
Burst	100 - 400µs	80 - 100 Hz, Bursts : 0,5 bis 10 Hz optimal 2 Hz	Limit of tolerance, motor threshold†, 3 to 6 times the sensory threshold*	20 to 45 minutes
Hifi	100 - 300µs	60 - 100 Hz	Limit of tolerance, motor threshold†, 3 to 6 times the sensory threshold*	15 to 20 minutes

* Sensory threshold=intensity at which the patient becomes aware of the electrostimulation; † motor threshold = intensity at which muscle contractions are first visible.

Web-appendix Table 3. TENS type used in the therapy sessions.

TENS type at each session, N(%)	TENS	Placebo TENS	P-value
Session 1	N = 107	N = 112	0.68
Low	0 (0%)	0 (0%)	
Burst	104 (97%)	110 (98%)	
High	3 (3%)	2 (2%)	
Session 2	N = 107	N = 112	0.62
Low	0 (0%)	0 (0%)	
Burst	106 (99%)	109 (97%)	
High	1 (1%)	3 (3%)	
Session 3	N = 107	N = 112	1.00
Low	0 (0%)	0 (0%)	
Burst	106 (99%)	110 (98%)	
High	1 (1%)	2 (2%)	
Session 4	N = 107	N = 112	0.74
Low	1 (1%)	0 (0%)	
Burst	106 (99%)	111 (99%)	
High	0 (0%)	1 (1%)	
Session 5	N = 107	N = 111	0.74
Low	1 (1%)	0 (0%)	
Burst	106 (99%)	110 (99%)	
High	0 (0%)	1 (1%)	
Session 6	N = 107	N = 110	0.49
Low	1 (1%)	0 (0%)	
Burst	106 (99%)	110 (100%)	
High	0 (0%)	0 (0%)	
Session 7	N = 106	N = 109	-
Low	0 (0%)	0 (0%)	
Burst	106 (100%)	109 (100%)	
High	0 (0%)	0 (0%)	
Session 8	N = 106	N = 109	0.49
Low	1 (1%)	0 (0%)	
Burst	105 (99%)	109 (100%)	
High	0 (0%)	0 (0%)	
Session 9	N = 106	N = 109	0.24
Low	1 (1%)	0 (0%)	
Burst	104 (98%)	109 (100%)	
High	1 (1%)	0 (0%)	

Web-appendix Table 4. Stimulation duration used in the therapy sessions.

Stimulation duration at each session, N(%)	TENS	Placebo TENS	P-value
Session 1	N = 107	N = 112	0.44
20 minutes	103 (96%)	110 (98%)	
45 minutes	4 (4%)	2 (2%)	
Session 2	N = 107	N = 112	0.62
20 minutes	106 (99%)	109 (97%)	
45 minutes	1 (1%)	3 (3%)	
Session 3	N = 107	N = 112	1.00
20 minutes	106 (99%)	110 (98%)	
45 minutes	1 (1%)	2 (2%)	
Session 4	N = 107	N = 112	1.00
20 minutes	107 (100%)	111 (99%)	
45 minutes	0 (0%)	1 (1%)	
Session 5	N = 107	N = 111	1.00
20 minutes	107 (100%)	110 (99%)	
45 minutes	0 (0%)	1 (1%)	
Session 6	N = 107	N = 110	-
20 minutes	107 (100%)	110 (100%)	
45 minutes	0 (0%)	0 (0%)	
Session 7	N = 106	N = 109	-
20 minutes	106 (100%)	109 (100%)	
45 minutes	0 (0%)	0 (0%)	
Session 8	N = 106	N = 109	-
20 minutes	106 (100%)	109 (100%)	
45 minutes	0 (0%)	0 (0%)	
Session 9	N = 106	N = 109	0.24
20 minutes	104 (98%)	109 (100%)	
45 minutes	2 (2%)	0 (0%)	

Web-appendix Table 5. Pulse duration used in the therapy sessions.

Pulse duration (µs), median (IQR)	TENS	Placebo TENS	P-value
Session 1	N = 107	N = 112	
	200 (200 to 225)	200 (200 to 225)	0.73
Session 2	N = 107	N = 112	
	200 (200 to 225)	200 (200 to 225)	0.48
Session 3	N = 107	N = 112	
	200 (200 to 225)	200 (200 to 225)	0.68
Session 4	N = 107	N = 112	
	200 (200 to 225)	200 (200 to 225)	0.68
Session 5	N = 107	N = 111	
	200 (200 to 225)	200 (200 to 225)	0.77
Session 6	N = 107	N = 110	
	200 (200 to 225)	200 (200 to 225)	0.81
Session 7	N = 106	N = 109	
	200 (200 to 225)	200 (200 to 225)	0.89
Session 8	N = 106	N = 109	
	200 (200 to 225)	200 (200 to 225)	0.89
Session 9	N = 106	N = 109	
	200 (200 to 225)	200 (200 to 225)	0.82

Web-appendix Table 6. Results of sensitivity analyses based on per-protocol and complete-cases datasets as compared to the main analysis based on the intention to treat principle. Displayed values are means and standard deviation unless otherwise specified.

Analysis set	TENS		Placebo TENS		Difference in means (95% CI)	p-value
ITT	n=108	2.20 ± 1.48	n=112	2.34 ± 1.69	-0.06 (-0.41 to 0.29)	0.74
Complete case	n=107	2.21 ± 1.48	n=111	2.33 ± 1.69	-0.05 (-0.40 to 0.31)	0.78
Per-protocol	n=105	2.20 ± 1.49	n=109	2.28 ± 1.65	0.00 (-0.35 to 0.36)	0.99

ITT: Intention-to-treat; CI: confidence interval. Difference in means and p values are adjusted for the WOMAC pain baseline value. WOMAC pain values are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity.

Web-appendix Table 7. Between-group comparisons of the primary outcome WOMAC pain at the end of treatment on the ITT population adjusted for one or all potential confounders considered.

Covariate used for adjustment	Mean difference (95% CI)	p-value
Number of treatment sessions	-0.1 (-0.4 to 0.3)	0.74
Use of chondroitin or glucosamine supplements	-0.1 (-0.4 to 0.3)	0.78
Use of any food supplement	-0.0 (-0.4 to 0.3)	0.78
Analgesic equivalence dose	-0.1 (-0.4 to 0.3)	0.73
Use of NSAIDs	-0.0 (-0.4 to 0.3)	0.78
Use of steroids	-0.0 (-0.4 to 0.3)	0.90
Received physiotherapy treatment other than TENS	-0.1 (-0.4 to 0.3)	0.77
Full adjustment	0.0 (-0.3 to 0.4)	0.96

ITT: intention-to.-treat, CI: confidence interval, [1] also adjusted for value at BL, [2] adjusted for subset as specified in meeting. 108 and 102 patients were analyzed in the TENS and placebo TENS groups, respectively. Difference in means and p-values are adjusted for the WOMAC pain baseline value. WOMAC pain values are normalized to a scale ranging from 0 to 10, with higher scores indicating a higher disease severity.