Hypoalgesic Effects of Transcutaneous Electrical Nerve Stimulation Combined With Joint Manipulation: A Randomized Clinical Trial

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Abstract

Objective: The objective of this study was to compare the hypoalgesic effects of isolated or combined use of transcutaneous electrical nerve stimulation (TENS) and cervical joint manipulation (JM) in asymptomatic participants.
Methods: One hundred and forty-four healthy participants aged 18 to 30 years old were randomly assigned to 1 of 4 groups (n = 36 per group): active TENS + active JM, active TENS + placebo JM, placebo TENS + active JM, and placebo TENS + placebo JM. Active or placebo TENS was applied to the dominant forearm. JM was applied to the C6-7 segments. The pressure pain threshold was measured pre- and postintervention and after 20 minutes on the forearm and tibialis anterior of the dominant side.
Results: Segmental hypoalgesia was greater in the group active TENS + active JM compared with active TENS + placebo JM ($P = .002$), placebo TENS + active JM ($P < .0001$), and placebo TENS + placebo JM ($P < .0001$). For the extrasegmental hypoalgesia, active TENS + active JM had greater hypoalgesic effect compared with active TENS + placebo JM ($P = .033$), placebo TENS + active JM ($P = .002$), and placebo TENS + placebo JM ($P < .0001$).
Conclusion: TENS and JM produced hypoalgesia when used alone and, when the treatments were combined, a higher segmental and extrasegmental hypoalgesic effect was obtained in asymptomatic participants. (J Manipulative Physiol Ther 2021;44:244-254)
Key Indexing Terms: *Musculoskeletal Manipulations; Transcutaneous Electric Nerve Stimulation; Pain Threshold; Neck; Spine*

Introduction

Transcutaneous electric nerve stimulation (TENS) is a technique used by health professionals to relieve a range of acute or chronic musculoskeletal pain conditions. It is a low-cost and easy-to-use therapy.[1-4] The gate control theory provided a theoretical rationale for the use of electrical stimulation in the management of pain and served as a basis for the development of the first TENS units.[5] This theory proposes that stimulation of large-diameter Aβ afferents inhibits the ascending transmission of noxious information carried by small-diameter afferent fibers (C and Aδ) on their way to the brain.[5-7] The use of TENS also promotes analgesia by activating the descending inhibitory pathways that originate in the periaqueductal gray (PAG) matter and in the rostral ventral medulla (RVM) to inhibit excitability of nociceptive neurons in the dorsal horn of the spinal cord.[7-12]

Currently, it is known that the main mechanism of TENS analgesic action occurs through the activation of opioid receptors in the central nervous system and in peripheral nociceptors,[7,8,10,11] in a frequency-dependent manner. Low-frequency (<10 Hz) TENS activates μ-opioid receptors, whereas high-frequency TENS (>50 Hz) activates δ-opioid receptors.[7]

Besides TENS, other nonpharmacologic techniques are often used for pain control. Among these, joint manipulation (JM) has become one of the most common forms of non-invasive treatment.[13,14] The term *manipulation/mobilization* has been defined by the American Physical Therapy Association Guide to Physical Therapist Practice as "a manual therapy technique comprised of a continuum of skilled passive movements that are applied at varying speeds and amplitudes, including a small amplitude/ high

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velocity therapeutic movement."[15] JM involves a high-velocity low-amplitude thrust.[16] During JM, the speed, the amplitude, and the movement direction can be controlled.[17,18]

Although numerous studies have reported immediate hypoalgesic effects on pain perception after JM,[19-21] the literature diverges if the hypoalgesic effect is local (segmental) or systemic (extrasegmental).[20,22] Segmental hypoalgesia is defined as a diminished pain at the treatment site or at spinal cord segment associated with the reported pain,[20,23] whereas extrasegmental hypoalgesia occurs in remote areas, far from the site of application of therapy.[20,24,25] According to a systematic review on the effect of JM on experimental pain induced in asymptomatic participants, local and systemic hypoalgesic effects were often reported; however, most studies that found an extrasegmental effect were not blinded.[20] However, regarding the application of TENS, few studies have investigated extrasegmental effects in asymptomatic participants. Chesterton et al. showed that the use of TENS produced an extrasegmental hypoalgesic effect maintained for 30 minutes in healthy individuals.[26] Other authors also found segmental and extrasegmental hypoalgesic effects in healthy participants after TENS application.[27]

Numerous authors have reported that JM generates afferent stimuli to the central nervous system by a stretching of the joint capsule, activating the PAG and producing analgesia through the activation of the non-opioid descending inhibitory pathways.[28-35] TENS and JM promote analgesia by activating the PAG; however, TENS activates the opioidergic whereas JM activates the noradrenergic system.[1,7,9,10,12,19,24,36] There is strong evidence that both TENS and JM increase the segmental[3,19-21,23.,26,27,32,37-41] and extrasegmental[19-21,26,27,37] pressure pain threshold (PPT) in asymptomatic participants. However, to our knowledge the combined effects of these 2 techniques have not been investigated. Then, it becomes relevant to verify if the combination of TENS and JM produces a higher segmental and/or extrasegmental hypoalgesia. We hypothesized that the combined use of TENS and JM would produce a higher hypoalgesic effect than the isolated use of each one of them. The objective of the present study was to compare the segmental and extrasegmental hypoalgesic effects of isolated or combined use of TENS and JM in asymptomatic participants.

Methods

This double-blind randomized trial was carried out at the physiotherapy clinic of the Catholic Salesian University Center Auxilium – Lins, São Paulo from May 2018 to January 2019 and the participants were recruited through oral and virtual communication on the grounds of the university. The study has been approved by the Research Ethics Committee of the Catholic Salesian University Center Auxilium (Unisalesiano-Araçatuba; CAAE: 76494117.5.3001.5379), São Paulo, on March 2018, and it was registered with clinicaltrials.gov before data collection (NCT03531541). The protocol of the present study was previously published[42] and this study followed the guidelines of the Consolidated Standards of Reporting Trials (http://www.consort-statement.org/).

After consenting to participate, the participants were stratified by sex to ensure equal numbers of men and women in each group (n = 36 per group) and were randomly assigned to 1 of 4 groups: active TENS + active JM, active TENS + placebo JM, placebo TENS + active JM, and placebo TENS + placebo JM. Participants were randomized using www.randomization.com, in which information was inserted (sample size, number of groups). The treatment assignments were randomly generated and placed in opaque, sequentially numbered envelopes by a researcher not involved in patient recruitment or randomization. The envelopes were stored in a secure cabinet that only the allocation investigator had access to, and were opened immediately before intervention allocation.[39,43]

Sample Size Calculation

The sample size was calculated a priori considering a difference of 100 kPa in the PPT values between groups, SD of 117 kPa,[39] power of 80%, significance level of 5%, and 4 treatment groups. A possible sample loss of up to 15% was considered, therefore, 36 participants were required per group (144 in total) (Minitab, v.17, State College, PA).

Participants

A total of 152 participants were selected for the study. Among these, 144 asymptomatic participants of both sexes between 18 and 30 years old with no pain complaints in the last 90 days agreed to participate in the study (Fig 1). Participants were excluded if they met the following criteria: surgery on the spine; spinal canal stenosis; vertebral fracture spondylolisthesis; cancer; acute infections; bleeding disorders; active tuberculosis; recent deep vein thrombosis; osteoporosis; rheumatologic, metabolic, and cardiovascular disease; stroke; headache; smoking; musculoskeletal injuries; alterations in skin sensitivity; cardiac pacemaker; women in menstrual period; pregnancy; use of painkillers, anti-inflammatory medication, or muscle relaxants in the last 48 hours; or participants who had prior experience with TENS or JM and exhibiting a positive vertebral artery test.[44,45]

Procedure

The participants were submitted to evaluation and then received active or placebo TENS. Next, the participants received active or placebo JM. After the procedure, there was a 20-minute interval. The participants were submitted

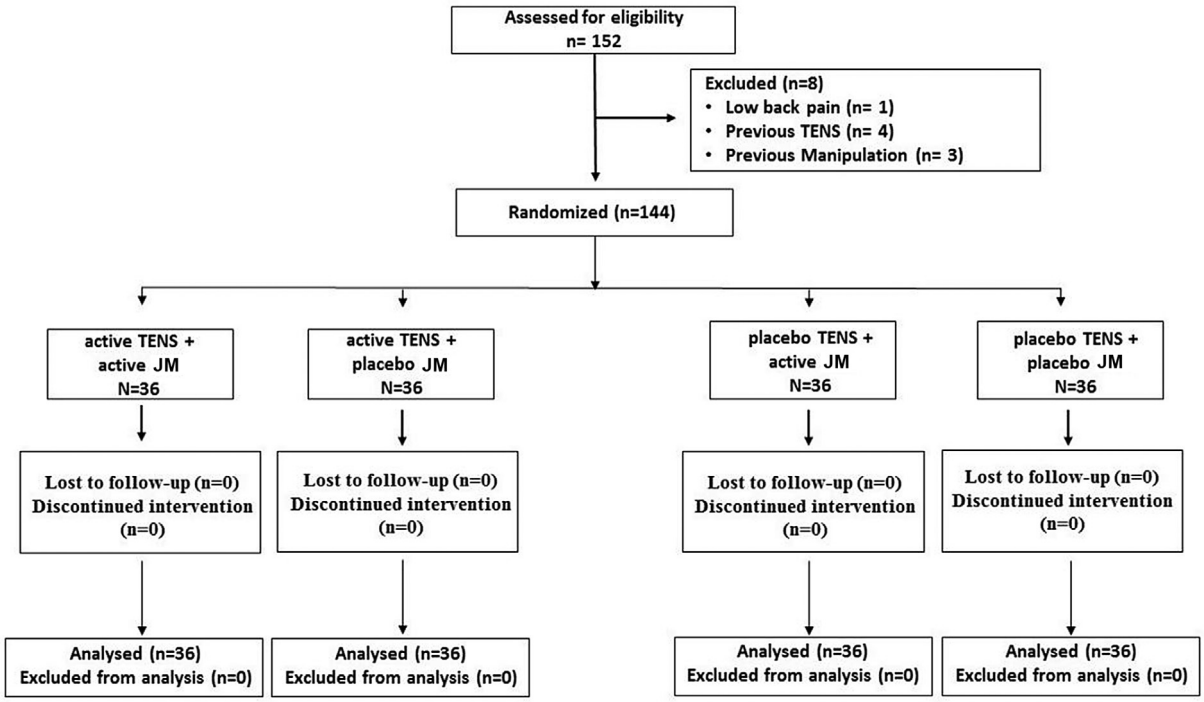

Fig 1. *Flow diagram.*

to a evaluation post interventions and a new evaluation was perfomed after 20 minutes of interventions. The experimental protocol timeline is shown in Fig 2.

Pressure Pain Threshold

The PPT was measured using digital algometer (Somedic Inc, Hörby, Sweden). The participants were positioned in a supine position for PPT recordings on the dominant forearm (primary outcome)[2,3,46] and on the tibialis anterior ipslateral to the dominant forearm (secondary outcome)[22,47] by a blinded evaluator. The order of interventions was also randomized on www.randomization.com. The participants' forearms were cleaned with mild soap and water. The PPT recording site was marked over the posterior region of the forearm, 10 cm below the lateral elbow epicondyle toward the third finger, with the forearm kept in pronation. Two TENS electrodes were placed 1 cm below the lateral epicondyle of the humerus and 10 cm above the region of the participant's dominant hand's radiocarpal joint, maintaining the region where the PPT was recorded between the 2 electrodes (Fig 3). The PPT was measured 3 times at 30-second intervals[22,39,47] to calculate the average value (baseline). The pressure was applied perpendicular to the skin at a rate of 40 kPa/s using a flat 1-cm^2 circular probe covered with 1 mm of rubber to minimize irritation of the skin.[2,3,46] Each participant had 1

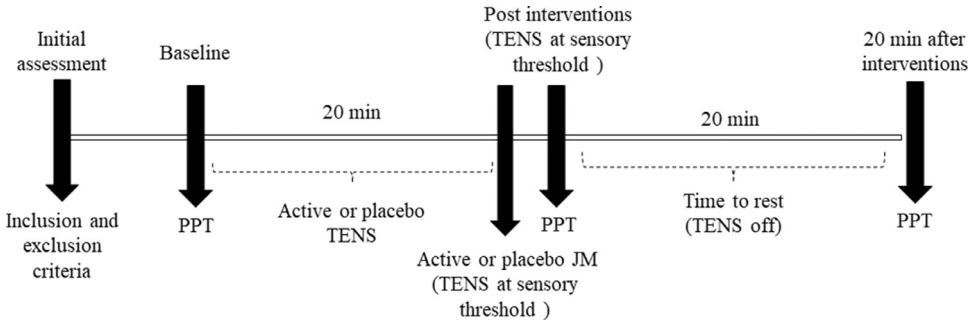

Fig 2. *Experimental protocol timeline. JM, joint manipulation; PPT, pressure pain threshold; TENS, transcutaneous electrical nerve stimulation.*

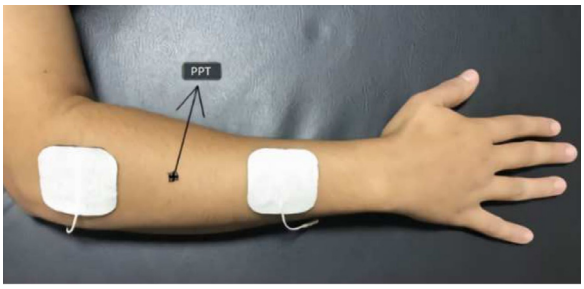

Fig 3. *Pressure pain threshold measurement site and transcutaneous electrical nerve stimulation placement. PPT, pressure pain threshold; TENS, transcutaneous electrical nerve stimulation.*

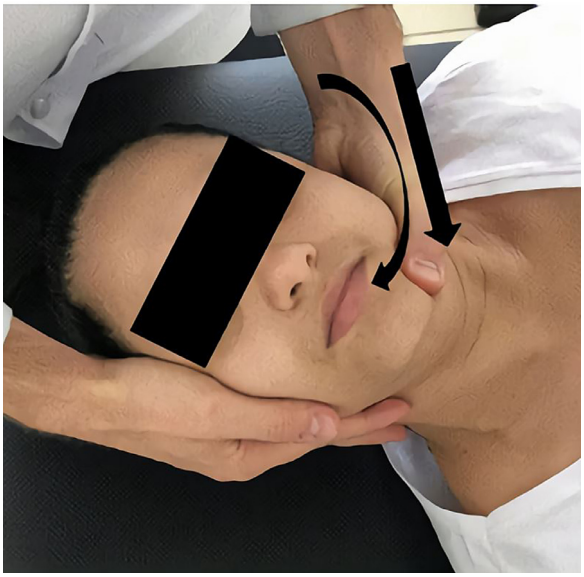

Fig 4. *Cervical joint manipulation performed at the C6-7 vertebrae.*

application of the PPT measurement on the upper trapezius to ensure that they understood the PPT concept before the data collection. The postintervention PPT evaluation was perfomed with TENS at sensory threshold.

Transcutaneous Electrical Nerve Stimulation

Two identical TENS units were used, 1 active and 1 placebo. The latter was specially developed for the study (Neurodyn Portable TENS, Ibramed, Amparo, São Paulo, Brazil). The active TENS unit was applied for 20 minutes with the participant in dorsal decubitus. Stimulation parameters were set at 100 Hz of frequency, pulse duration of 100 μs, and a strong but comfortable intensity, as dictated by each participant. Participants were asked about TENS sensation every 5 minutes. If the intensity decreased, it was increased again to a strong but comfortable level tolerated by the participant.[1,12,39,48] For the application of the placebo TENS unit, the stimulation parameters were set at 100 Hz of frequency and pulse duration of 100 μs at sensory threshold intensity during 20 minutes; however, it was active for the first 30 seconds, then the current ramped down to zero stimulus over the next 15 seconds.[3,12,39,49]

This device facilitates blinding of participants to eliminate expectation bias and determine the true efficacy of TENS for use in clinical populations.[49] The placebo TENS unit was applied for 20 minutes. The participants were told they may or may not feel a sensation during the intervention.[48] Every 5 minutes, investigator 1 asked the participant if he or she was feeling comfortable to maintain the same pattern and level of attention in the application of active TENS, without increasing the current intensity.

Cervical Joint Manipulation

Before cervical JM, after 20-minute application of active TENS, investigator 1 reduced the intensity to the sensory threshold. For cervical JM, investigator 2 (who was blinded to the application of TENS) positioned the middle phalange of the second finger laterally on the joint processes of the C6-7 vertebrae. With the contralateral hand he supported the opposing face of the participant by performing a tilt up to the C6-7 segment and contralateral rotation up to the tissue barrier to carry out the impulse quickly and short (Fig 4).[14,22.,40,50] Participants were manipulated up to 2 times according to cavitation. If an audible pop or cavitation was not heard during the first manipulation, the participant was repositioned, and a second manipulative attempt was made.[22,41,51] The manipulation of segment C6-7 was chosen owing to the metameric relationship with the forearm region, where PPT records were performed and where TENS was applied.

Placebo cervical JM was conducted with the participant positioned the same way described for active cervical JM; however, the position was maintained for 15 seconds, as suggested by some authors who used a placebo group for studies with JM.[33,50,52,53] Both procedures were carried out by a physiotherapist with more than 5 years' clinical experience using these techniques.

Statistical Analysis

Data were analyzed using SPSS version 20.0 for Windows (IBM Corporation, Armonk, NY). The comparability of study groups at baseline for sex, age, body mass index, or other demographics was assessed by using the 1-way analysis of variance, the Kruskal-Wallis test, or the Fisher exact test. The average of the 3 PPT scores recorded at each point was used for analyses. Kolmogorov-Smirnov tests showed that data were normally distributed; therefore, parametric tests were used to analyze the data. Percentage

of change (variation from baseline values) was analyzed using between-within groups analysis of variance and post hoc Tukey tests. Positive percentage values of PPT represent hypoalgesia, and negative values represent hyperalgesia. Significance was set at $P < .05$. The chi-square test was used to compare blinding of the groups against an expected result of 50:50 blinding (ie, chance). Statistical significance was set at $P < .05$.

Results

Table 1 shows the demographic characteristics of participants. All study groups were comparable in sex, age, body mass index, ethnicity, education, upper limb dominance and marital status. There was no important adverse events or side effects in each intervention group.

The raw data of forearm PPT measurements (mean ± standard error of the mean [SEM]) for each group are shown in Table 2. Figure 5 shows the mean PPT percentages of change (± SEM) in the forearm for each experimental group. There was a statistically significant difference for the forearm over time ($P = .0001$) and an interactive effect between time and groups ($P = .002$), where active TENS + active JM showed a significant increase in PPT compared with active TENS + placebo JM (between-group difference = 14.9 kPa, CI 95% = 5.74-24.14, $P = .002$), placebo TENS + active JM (between-group difference = 16.6 kPa, CI 95% = 7.49-25.89, $P = .0001$), and placebo TENS + placebo JM (between-group difference = 31.1 kPa, CI 95% = 21.96-40.36, $P = .0001$) postinterventions. There was an increase in the PPT of active TENS + placebo JM compared with placebo

Table 1. *Demographic Characteristics of Participants in the Study*

	Groups				
Characteristics	Active TENS + Active JM (n = 36)	Active TENS + Placebo JM (n = 36)	Placebo TENS + Active JM (n = 36)	Placebo TENS + Placebo JM (n = 36)	*P* Value
Sex n (%)					
Male	18 (50%)	18 (50%)	18 (50%)	18 (50%)	1.000[c]
Female	18 (50%)	18 (50%)	18 (50%)	18 (50%)	
Age, years (mean ± SD)	23.3 ± 3.6	21.4 ± 3.1	21.6 ± 2.9	22.5 ± 3.6	.101[b]
BMI, kg/m^2 (mean ± SD)	24.9 ± 3.2	24.9 ± 4.5	24.1 ± 3.5	25.0 ± 3.7	.698[a]
Ethnicity (%)					
White	27 (75%)	24 (66.6%)	30 (83.3%)	33 (91.6%)	.816[c]
Others	9 (25%)	12 (33.3%)	6 (16.7%)	3 (8.4%)	
Education (%)					
High school or less	34 (94.4%)	33 (91.6%)	34 (94.4%)	33 (91.6%)	.697[c]
Some college or above	2 (5.6%)	3 (8.4%)	2 (5.6%)	3 (8.4%)	
Upper limb dominance (%)					
Right	31 (86.1%)	32 (88.8%)	30 (83.3%)	31 (86.1%)	.927[c]
Left	5 (13.9%)	4 (11.2%)	6 (16.7%)	5 (13.9%)	
Marital status (%)					
Not married	32 (88.8%)	33 (91.6%)	35 (97.2%)	33 (91.6%)	.902[c]
Married	4 (11.2%)	3 (8.4%)	1 (2.8%)	3 (8.4%)	

BMI, body mass index; *JM*, joint manipulation; *TENS*, transcutaneous electrical nerve stimulation.
[a] Data that were assumed to be normally distributed were analyzed with the 1-way analysis of variance.
[b] Data that were not normally distributed, and, subsequently group differences were analyzed with the Kruskal-Wallis test.
[c] Categorical data were analyzed with the Fisher exact test.

Table 2. *Mean ± SEM Raw PPT Scores for All Points, for Each Group in the Forearm Measurement Site*

	Time		
Group	Baseline	Postintervention	After 20 Min
Active TENS + active JM	241.2 ± 15.0	326.2 ± 19.5	279.3 ± 20.9
Active TENS + placebo JM	257.5 ± 15.4	314.3 ± 19.9	275.3 ± 16.9
Placebo TENS + active JM	254.9 ± 18.1	299.3 ± 18.6	244.0 ± 18.9
Placebo TENS + placebo JM	278.4 ± 16.7	292.2 ± 17.1	254.1 ± 15.8

Note: All values are expressed in kPa.
JM, joint manipulation; *SEM*, standard error of the mean; *TENS*, transcutaneous electrical nerve stimulation.

TENS + placebo JM (between-group difference = 16.2 kPa, CI 95% = 7.02-25.42, $P = .001$) postinterventions. Placebo TENS + active JM showed a significant increase in PPT postinterventions compared with placebo TENS + placebo JM (between-group difference = 14.4 kPa, CI 95% = 5.27-23.67, $P = .002$). For the forearm measurements after 20 minutes of intervention, active TENS + active JM showed a significant increase in PPT compared with placebo TENS + active JM (between-group difference = 12.5 kPa, CI 95% = 2.41-22.58, $P = .015$) and to placebo TENS + placebo JM (between-group difference = 16.7 kPa, CI 95% = 6.69-26.85, $P = .001$). Active TENS + placebo JM showed a significant increase in PPT compared with placebo TENS + placebo JM (between-group difference = 13.2, CI 95% = 3.19-23.35, $P = .010$).

No significant difference was observed regarding PPT after 20-minute application of active TENS + active JM compared with active TENS + placebo JM ($P = .494$), active TENS + placebo JM compared with placebo TENS + active JM ($P = .080$), and placebo TENS + active JM compared with placebo TENS + placebo JM ($P = .403$).

Mean ± SEM raw PPT scores of tibialis anterior muscle for all measurement times for each group are shown in Table 3. Figure 6 shows percentage of changes in PPT (means ± SEM) on the tibialis anterior muscle over time.

There was a statistically significant difference for the tibialis anterior muscle measurements over time ($P = .0001$) and an interactive effect between time and group ($P = .0001$) where active TENS + active JM showed a significant PPT increase compared with active

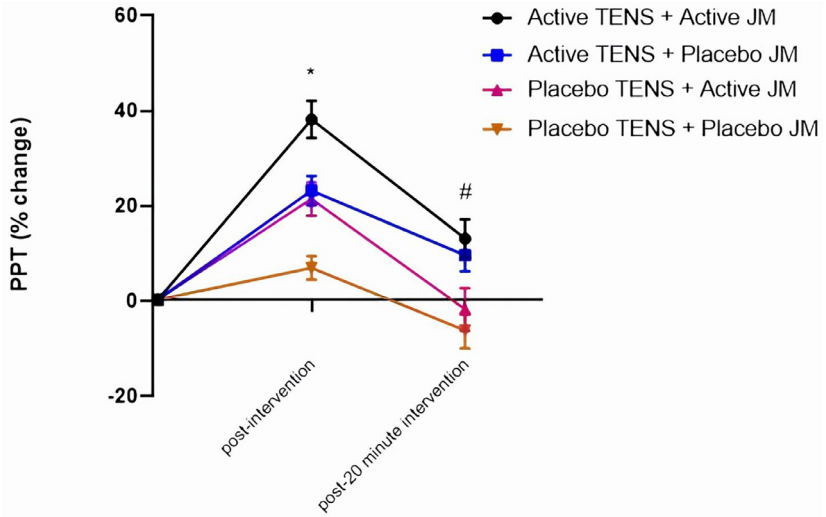

Fig 5. *Percentages of changes in pressure pain threshold on forearm of experimental groups (mean ± standard error of the mean). Baseline differences. * indicates active transcutaneous electrical nerve stimulation (TENS) + active joint manipulation (JM) significantly different compared with active TENS + placebo JM (P = .002), placebo TENS + active JM (P = .0001) and to placebo TENS + placebo JM (P = .0001).* indicates active TENS + placebo JM significantly different compared with placebo TENS + active JM (P = .002) and to placebo TENS + placebo JM (P = .001). * indicates placebo TENS + active JM significantly different compared with placebo TENS + placebo JM (P = .002). # indicates active TENS + active JM significantly different compared with placebo TENS + active JM (P = .015) and to placebo TENS + placebo JM (P = .001). # indicates active TENS + placebo JM significantly different compared with placebo TENS + placebo JM (P = .010). JM, joint manipulation; PPT, pressure pain threshold; SEM, standard error of the mean; TENS, transcutaneous electrical nerve stimulation.*

Table 3. *Mean ± SEM Raw PPT Scores for All Time Points, for Each Group in the Tibialis Anterior Muscle Measurement Site*

	Time		
Groups	Baseline	Postintervention	After 20 min
Active TENS + active JM	356.4 ± 26.5	414.8 ± 26.0	387.5 ± 25.8
Active TENS + placebo JM	399.5 ± 25.5	443.8 ± 26.4	415. 5 ± 28.0
Placebo TENS + active JM	378.7 ± 21.7	401.6 ± 23.5	365.6 ± 23.5
Placebo TENS + placebo JM	401.6 ± 27.8	418.3 ± 26.4	427.7 ± 27.8

JM, joint manipulation; *PPT*, pain pressure threshold; *SEM*, standard error of the mean; *TENS*, transcutaneous electrical nerve stimulation.
Note: All values are expressed in kPa.

TENS + placebo JM (between-group difference = 8.08 kPa, CI 95% = 0.64-15.51, $P = .033$), placebo TENS + active JM (between-group difference = 11.7 kPa, CI 95% = 4.34-19.21, $P = .002$), and placebo TENS + placebo JM (between-group difference= 15.1 kPa, CI 95% = 7.75-22.63, $P = .0001$) for post-intervention measurements.

No significant difference was observed between active TENS + placebo JM and placebo TENS + active JM ($P = .328$), between active TENS + placebo JM and placebo TENS + placebo JM ($P = .061$), and between placebo TENS + active JM and placebo TENS + placebo JM ($P = .365$). For the 20-minute intervention measurements, active TENS + active JM showed a significant PPT increase compared with placebo TENS + active JM (between-group difference = 13.6 kPa, CI 95% = 5.34-21.99, $P = .001$). Placebo TENS + placebo JM showed a significant PPT increase compared with placebo TENS + active JM (between-group difference = 10.3 kPa, CI 95% = 2.01-18.65, $P = .015$). After 20 minutes of interventions, no significant differences were found between active TENS + active JM compared with active TENS + placebo JM ($P = .059$), placebo TENS + active JM compared with placebo TENS + placebo JM ($P = .430$), active TENS + placebo JM compared with placebo TENS + active JM ($P = .185$), and active TENS + placebo JM compared with placebo TENS + placebo JM ($P = .267$).

Blinding Assessment

The assessor correctly identified the treatment groups in 20.16% of the cases (14 of 144), being blinded 79.84% of the time, indicating that the blinding was successful (chi-square, $P < .0001$). The researcher responsible for JM was able to identify the participants

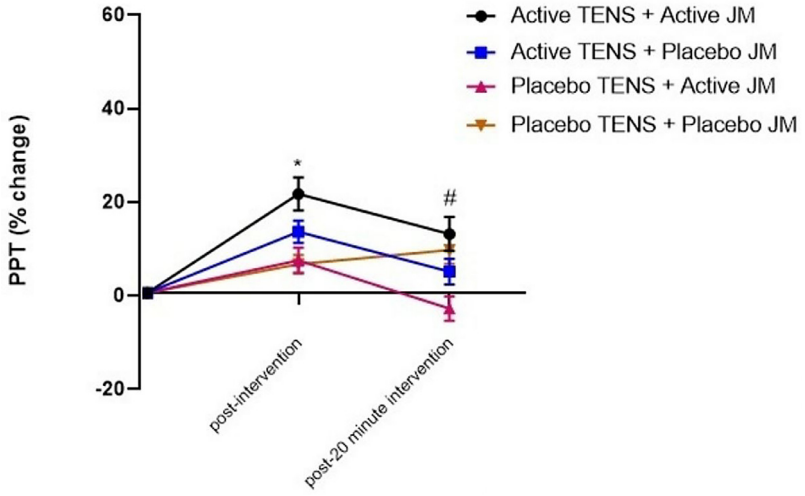

Fig 6. *Percentages of changes in pressure pain threshold on tibialis anterior muscle of experimental groups (mean ± standard error of the mean). Baseline differences. * indicates active transcutaneous electrical nerve stimulation (TENS) + active joint manipulation (JM) significantly different compared with active TENS + placebo JM (P = .033), placebo TENS + active JM (P = .002), and placebo TENS + placebo JM (P = .0001) post-intervention. # indicates active TENS + active JM significantly different compared with placebo TENS + active (P = .001). # indicates TENS placebo + MA placebo significantly different compared with placebo TENS + active JM (P = .015) after 20-minute intervention. JM, joint manipulation; SEM, standard error of the mean; TENS, transcutaneous electrical nerve stimulation.*

who received active TENS in 7.92% of the cases (11 of 72), being blinded 92.08% of the time, indicating that the blinding was successful (chi-square test, $P < .0001$). Of the 72 participants who received placebo TENS, 9 were right, 53 wrong, and 10 said they did not know, indicating that the blinding was successful (chi-square, $P < .0001$). Of the 72 participants who received placebo JM, 12 were right, 43 wrong, and 17 did not know 17, suggesting that blinding was generally preserved (chi-square, $P < .0001$).

Discussion

The hypoalgesic effect produced by TENS[37,39,48,54,55] and JM[32,40-41,52] have been demonstrated in humans; however, this is the first study to assess the combined effects of both TENS and JM in asymptomatic participants. Our results showed that when used together, TENS and JM produced a greater hypoalgesic effect than when using either alone in asymptomatic participants.

A possible explanation for these results is that when these 2 treatment methods (TENS and JM) are combined, the activation of different inhibitory descending pathways may produce a greater pain inhibitory effect. TENS activates the inhibitory descending pathways that originate in the PAG and RVM.[7,8,10,12,36,56] Analgesia generated by high-frequency TENS is reversed by the use of naloxone, indicating that the analgesic effect during the application involves the release of endogenous opioids.[7,11] There was no change in the levels of serotonin and noradrenaline with high-frequency TENS (100 Hz) in the dorsal horn of the spinal cord of rats.[57] According to numerous studies, JM also activates PAG[9,24,28,34,35]; however, the initial hypoalgesic effect of JM is not reversed by the administration of naloxone.[9] The authors determined that the analgesic effects of joint manipulation were affected by the blockade of 5-Hydroxytryptamine 1A (5HT1A) and α2-adrenergic receptors, suggesting that JM activates the descending inhibitory pathways and releases inhibitory neurotransmitters, such as noradrenaline and serotonin, which modulate the ascending nociceptive transmission, different from those activated by TENS.

Our results also showed that the combined use of TENS and JM produced higher segmental and extrasegmental hypoalgesic effect when compared with the other groups, probably because of the added effect of the descending inhibitory pathways that both methods activate. Some studies have found enhanced hypoalgesic effect using TENS with cryotherapy,[58] stretching[4] and heat,[59] however not when combined with conditioned pain modulation (CPM).[3] Liebano et al reported that the possible explanation for no additional increase in the hypoalgesia when combining both modalities is that, when activating CPM, the descending pathways from medullary reticularis nucleus dorsalis would produce a large inhibitory effect on T cells in the dorsal horn of the spinal cord. Thus, when TENS activates the descending pathways from PAG/RVM, a maximal hypoalgesic effect was already obtained by CPM activation producing no additional hypoalgesia. However, when CPM was combined with cervical manipulation, increased analgesia was found in patients with lateral epicondylalgia. The authors point out that both interventions activate inhibitory descending pathways that use serotonin and norepinephrine and that the combination of both therapies potentiated the analgesic effect.[60]

Regarding TENS alone, our study showed that a more significant hypoalgesic effect of active TENS + placebo JM compared with placebo TENS + placebo JM post-interventions for the segmental measurement, demonstrating that the isolated application of TENS produced greater hypoalgesic effect compared with placebo, corroborating several studies that compared TENS with placebo.[39,48,54,55]

The results obtained with the isolated application of JM showed a significantly increased hypoalgesic effect of placebo TENS+ active JM compared with placebo TENS + placebo JM after interventions for the segmental stimulation, corroborating numerous studies that demonstrated that JM alone may increase the hypoalgesic response compared with placebo.[32,40-41,52] Some systematic reviews have also showed increased hypoalgesic effect in favor of JM compared with placebo or control in asymptomatic participants,[19-21] which appeared to act more on pain induced by pressure than by temperature. In a recent systematic review, the authors concluded that cervical JM enhanced the hypoalgesic effect compared with lumbar and thoracic JM.[21] In another study, however, when cervical JM was combined with lumbar JM, there was no hypoalgesic effect on the tibialis anterior, upper trapezius, lumbar paravertebral muscles, and forearms in healthy participants.[22] However, the authors used only a measure of the PPT in each point and performed manipulations on cervical and lumbar region in the same session. Nonetheless, some authors reported that the speed and the site of the JM may elicit different neurochemical responses indicative of different descending pain modulation mechanisms.[61] Our study also observed an increased extrasegmental hypoalgesic effect produced by the combined use of TENS and JM, but not by either treatment alone, evidencing that both methods increased the likelihood of activating extrasegmental mechanisms. According to a systematic review on the effect of JM on experimentally induced pain in asymptomatic participants, local and systemic hypoalgesic effects were often observed. However, the authors noted that most of the studies included in the review did not use blinded assessors.[20] Thus, our study sought to fill this gap in the clinical literature. Regarding the extrasegmental effect produced by TENS, only a single study in a systematic review[62] demonstrated a significant effect in asymptomatic participants.[26] In the study, the authors observed

that the use of low-frequency TENS (4 Hz) produced a significant extrasegmental hypoalgesic effect compared with the application of high-frequency TENS (110 Hz).[26]

The present study has shown a significant increase of segmental hypoalgesic effect after 20 minutes of active TENS + active JM compared with placebo TENS + active JM and placebo TENS + placebo JM. For the extrasegmental stimulation, we found a significant increase of hypoalgesic effect after 20 minutes of intervention produced only by active TENS + active JM compared with placebo TENS + active JM.

There was no statistical difference for extrasegmental hypoalgesia postintervention and after 20 minutes between active TENS + placebo JM and placebo TENS + active JM, nor between active TENS + placebo JM and placebo TENS + placebo JM. Perhaps the most surprising finding of our study is a significant extrasegmental hypoalgesic effect produced by placebo TENS + placebo JM compared with placebo TENS + active JM after 20 minutes of intervention; however, this difference may have occurred at random.

Limitations

The study sample included asymptomatic participants; therefore, future clinical studies should be conducted to confirm these results in symptomatic patients. Owing to the nature of the interventions it was not possible to blind the assessors who applied TENS and JM; however, efforts were made to reduce bias of the investigator responsible for TENS application using a pre-established design, which would depict the effectiveness and the expectations regarding TENS application to all participants in a similar manner. In addition, this study used placebo manipulation. Although this type of placebo is often used in studies with manipulation/manual therapy,[33,53] studies need to be carried out to validate this procedure.

The findings of the present study showed that the combined use of TENS and JM produced a higher segmental and extrasegmental hypoalgesia. However, these findings could only be considered for pain-free asymptomatic participants and they could not be directly translated to the clinic population, because their characteristics may differ from asymptomatic participants. Therefore, clinical studies, using TENS and JM, should be performed to confirm these results in patients experiencing pain.

Conclusion

These results suggest that both TENS and JM produced hypoalgesia when used alone and, when the treatments were combined, a higher segmental and extrasegmental hypoalgesic effect was obtained in asymptomatic participants.

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The authors received no specific funding for this work. The authors have no conflict of interest to declare.

Contributorship Information

Concept development (provided idea for the research): J.D.T., R.E.L.
Design (planned the methods to generate the results): J.D.T., M.A.G.S., A.C.S.C.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): J.D.T., R.E.L., É.P.R.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): J.D.T., A.C.S.C.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): J.D.T., É.P.R., R.E.L.
Literature search (performed the literature search): J.D.T.
Writing (responsible for writing a substantive part of the manuscript): J.D.T., É.P.R., R.E.L.
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Practical Applications

- The isolated use of TENS produced local hypoalgesia.
- Joint manipulation alone also produced local hypoalgesia.
- The combined use of TENS and joint manipulation produced a greater local and distant hypoalgesia.

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