OPEN ACCESS
Saudi Journal of Biomedical Research
Abbreviated Key Title: Saudi J Biomed Res
ISSN 2518-3214 (Print) |ISSN 2518-3222 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://scholarsmepub.com/sjbr/

Original Research Article

Transcutaneous Electrical Nerve Stimulation in Patients with Cancer-Related Pain: A Systematic Review

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DOI:10.21276/sjbr.2019.4.7.2 | **Received:** 20.07.2019 | **Accepted:** 27.07.2019 | **Published:** 30.07.2019

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Abstract

Objective: This study aimed to perform a systematic review, in order to investigate the effects of a non-pharmacological therapy (TENS) in cancer pain through clinical trials. ***Methods:*** 208 studies were identified in those databases, after title and abstract analysis, 198 studies were excluded. A total of 10 studies were selected for full-text analysis. Six papers were excluded based on exclusion criteria, resulting in 4 studies included for this systematic review. Standardized forms were used for analysis. Risk of bias was assessed with the "Cochrane Collaboration" tool, which assess five different domains. ***Results:*** Selected studies were randomized clinical trials that investigated the use and/or feasibility of transcutaneous electrical nerve stimulation on patients suffering from cancer-related pain. However, studies had a high divergence regarding sample, methodological design, treatment parameters, and outcomes assessed. Two studies, one involving pain related to breast cancer treatment and other investigating TENS on palliative care, showed no difference from placebo. Other two manuscripts report positive effects on pain, one on cancer-related bone pain and a second on cancer-related postoperative pain. ***Conclusion:*** We concluded that there is no sufficient evidence showing that TENS is effective for treating cancer-related pain. Additional research, with larger sample sizes, sample homogeneity and randomization and that investigate potential side effects is needed for a better assessment of TENS viability for the treatment of cancer-related pain.

Keywords: TENS; Pain; Cancer.

INTRODUCTION

Cancer is currently one of the most devastating diseases, affecting the life of many people around the world. There were 14.1 million new cancer cases and 32.6 million people living with cancer in 2012 worldwide [1]. The World Health Organization (WHO) estimates an increase on incidence to 27 million cases of cancer by the year 2030. Despite advances in surgical and radiation treatments, chemotherapy continues to be an important therapeutic option for different malignancies, but it is still associated with severe side effects [2].

WHO estimates that 4 million people suffer from cancer-related pain throughout the world, this includes pain associated with the disease itself, its treatment modalities and its comorbidities. Studies reveal that the-prevalence of pain is between 24 and 60% in patients undergoing treatment for cancer [3-5] and 75% and 90% in advanced cancer patients [6]. Thus, pain is a frequent and distressing symptom in cancer patients.

Treatment for cancer pain is focused on eliminating or reducing cancer-related pain through pharmacological interventions (opioid analgesics, antidepressants, and anticonvulsants). However, these pharmacological agents induce severe side effects that contribute to reduction in the quality of life of cancer patients such as nausea and vomiting, constipation, drowsiness, dizziness and sedation [7-11].

Cancer-related pain, originated from either the disease or its treatment, is a public health issue worldwide, and to elucidating therapeutic alternatives less aggressive and invasive for pain management is a challenge to increase quality of life of patients suffering with the problem [12].

Other strategies, besides pharmacological treatment, may be used for pain control. Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological, non-invasive therapeutic intervention which involves the application of electric current on the skin surface for reducing acute and chronic pain [13]. Its effectiveness has been shown in a variety of clinical cases, and it has been increasingly used in patients with cancer-related pain, due to its low cost, easy application, few side effects or contraindications, safety and for enabling user's autonomy over pain control [14]. However, it is still necessary to gather more conclusive evidence regarding its efficacy in patients with cancer-related pain [15].

There's a growing rate of people with cancer who are subjected to chemotherapy treatments, which often results in pain that is mostly treated with pharmacological treatments for pain relief, with other severe side effects. This study aimed to perform a systematic review on the current evidence from clinical trials investigating the use of TENS for treatment of cancer-related pain.

METHODS

Data Sources and Searches

Searches were performed in seven scientific literature databases (Internet sources): Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences (LILACS), PEDro, PubMed, Science Direct, Scientific Eletronic Liberary Online (SciELO) and ScinFinder, using different combinations of the keywords. Mesh term "neoplasms" was used to identify the disease. While the Mesh term "Transcutaneous Electric Nerve Stimulation" and their synonyms (electrical stimulation, transcutaneous) OR (stimulation, transcutaneous electrical) OR (transcutaneous electrical stimulation) OR (percutaneous electric nerve stimulation) OR (percutaneous electrical nerve stimulation) OR (transdermal electrostimulation) OR (electrostimulation, transdermal) OR (transcutaneous electrical nerve stimulation) OR (transcutaneous nerve stimulation) OR (nerve stimulation, transcutaneous) OR (stimulation, transcutaneous nerve) OR (electric stimulation, transcutaneous) OR (stimulation, transcutaneous electric) OR (transcutaneous electric stimulation) OR (TENS) OR (electroanalgesia) OR (analgesic cutaneous electrostimulation) OR (cutaneous electrostimulation, analgesic) OR (electrostimulation, analgesic cutaneous) were used to represent the electric current. Databases were searched for studies performed in the period up to and including February 2019. The structured search strategy was designed to include any clinical trial that investigated the use or feasibility of Transcutaneous Electric Nerve Stimulation in cancer-related pain.

Study Selection

An analysis of titles and abstracts from the resulting list of papers was performed independently by two investigators (R.G.A and S.S.S) responsible for selection according to pre-established criteria. Cases of disagreement were analyzed and discussed with a third investigator (F.M.A or J.M.S.). The following inclusion criteria were used: randomized clinical trials, written in English and published until August 2017. The following exclusion criteria were used: studies in animals, review articles, meta-analyses, conference proceedings, editorials/letters, retrospective cohort study and case reports.

Data extraction and Quality Assessment

Data were extracted by two investigators (R.G.A. and S.S.S) independently, and checked by a third reviewer (F.M.A), using standardized forms. Extracted information included data referent to sample, intervention and outcomes.

This systemic review was performed by using the software Review Manager 5.3. Risk of bias was assessed with the Cochrane Collaboration's tool by two reviewers (R.G.A and S.S.S.). Therefore, five domains were assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting). Each of them was classified as "low risk", "high risk" or "unclear risk".

RESULTS

Study Selection

By searching the selected Mesh terms, 208 studies were identified in seven scientific databases used for this review. After title and abstract analysis, 198 articles were excluded. A total of 10 studies were selected for a full-text review. Additionally, 6 articles met the exclusion criteria and were removed, resulting in 4 studies included in this systematic review. A flow chart illustrating the progress of study selection and the number of studies at each stage is shown (Figure-1).

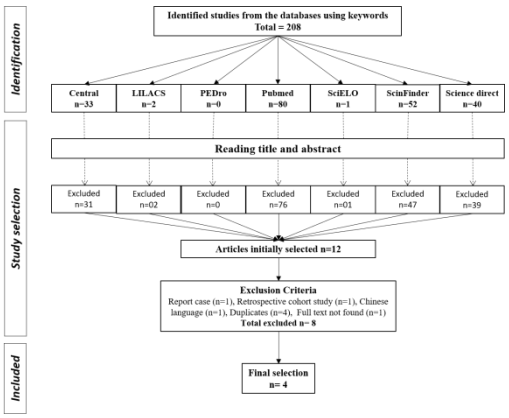

Fig-1: Flow chart illustrating selection of studies for systemic review

Characteristics of Included Studies

Four studies were included for the systematic review [16-19]. Those selected studies evaluated the use or feasibility of Transcutaneous Electric Nerve Stimulation in patients with cancer-related pain through randomized clinical trials. One study was developed in China, which included patients aging between 18 and 60 years [19]. The other three trials were conducted in the UK and included patients over the age of 18. When comparing those studies, distinct characteristics were observed in the selection of the population, eligibility, exclusion criteria, non-pharmacological intervention groups, intervention application, features of TENS and outcome measures, as detailed in Table-1.

Gadsby *et al*., [16] performed a study with fifteen patients of both sexes, diagnosed with terminal cancer, aiming to determining the potential role of acupuncture-like TENS for improving quality of life in patients in a palliative-care setting. Robb *et al*., [17] performed a study with women, mean age of 58 years, investigating the effect of self-applied, non-pharmacological interventions for chronic pain caused by breast cancer treatments. Bennet *et al*., [18] performed study with patients of both sexes, mean age of 72 years, investigating the feasibility of TENS intervention performed at the clinic, for patients suffering from bone metastasis cancer. Liu *et al.*, [19] performed a study with ninety-two patients of both sexes, scheduled for supratentorial craniotomy, investigating the anaesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation (TEAS) during supratentorial tumour resection for postoperative recovery and side effects.

Table-1: Characteristics of included studies

Characteristics	**Robb *et al.*,** [17]	**Bennett *et al.*,** [18]	**Gadsby *et al.*,** [16]	**Liu *et al.*,** [19]
Population	49 women with breast cancer	24 patients, both sexes, with bone metastasis cancer	15 patients, both sexes, diagnosed with terminal cancer	92 patients, both sexes, scheduled for supratentorial craniotomy
Eligibility	Patients aging over 18, history of breast cancer and chronic pain for at least six months	Patients aging over 18, painful bone metastasis and estimated survival of more than 4 weeks	Patients aging between 35 and 75, from caucasian origin, with no pain and / or nausea and vomiting symptoms	Patients aging between 18 and 60, with physical status I or II according to the American Society of Anesthesiologists
Exclusion Criteria	Evidence of recurrent cancer, inability to follow the author's instructions, had pain due to a neurological condition (e.g., stroke), had complete lack of skin sensation in the areas to be treated, or had previous experience of TENS or TSE	Pregnant patients, patients with pacemakers, epilepsy, and abnormal sensation at the pain site (such as allodynia), changes to their medication within 48 hours prior to baseline	Patients unwilling to provide informed consent, hose too ill to cope with 30 min of treatment, patients with pacemakers, premenopausal women, patients with vomiting due to intestinal obstruction or raised intracranial pressure or iatrogenic causes and those who had previously received TENS or ALTENS treatment.	Patients in pregnancy or lactation; with the complication of severe respiratory and circulatory system diseases; long-term heavy smokers; patients with body mass index >35 kg/m^2; emergency patients. Patients with operation time >8 h and operative blood loss >2500 mL.
Type of study	Randomized controlled clinical trial with crossover design.	Randomized controlled clinical trial with crossover design.	Randomized controlled clinical trial.	Randomized blind controlled clinical trial.
Non-pharmacological intervention groups	G1: TENS, TSE, Placebo G2: TENS, Placebo, TSE G3: TSE, TENS, Placebo G4: TSE, Placebo, TENS G5: Placebo, TSE, TENS G6: Placebo, TENS, TSE	G1: TENS, Placebo G2: Placebo, TENS	G1: standard treatment G2: standard plus ALTENS G3: standard plus placebo	G1: TEAS group G2: sham group
Intervention application	Patients used each treatment at home for three weeks, with an one-week ''washout''	60 minutes of TENS or placebo. 2 to 7 days later TENS or placebo observing order of the	Five consecutive daily treatments	Patients received preoperative TEAS starting 30 min before anaesthesia induction, maintained throughout the

	period, observing order of the group. The frequency of treatment depended on each patient	group		operation and terminated at the end of surgery.
Features of TENS	TENS selected to operate in ‘‘continuous mode’’ with a ‘‘strong but comfortable’’ paresthesia. But patients were encouraged to manipulate TENS parameters to find the optimal treatment parameters for their pain.	Pulse width of 200 microseconds, pulse frequency of 80 Hz and Intensity increased until the TENS sensation was strong but comfortable.	Pulse rate set at 2 pulses per second with a symmetrical biphasic pulsewave in continuous mode. Pulse width 200 ms. Amplitude setting at 2.5 on the unit output scale; timer set at 30 min as the duration of each treatment.	A dense-disperse frequency of 2/100 Hz (alternated once every 3 s; 0.6 ms at 2 Hz and 0.2 ms at 100 Hz). The intensity of stimulation was set at 4.89±2.15, 6.79±3.51, 7.04±3.35 and 5.61±2.13, respectively, according to the maximal tolerance of patients and maintained throughout the operation.
Outcome measures	Brief Pain Inventory (BPI) Short Form and Hospital Anxiety and Depression (HAD), range of movement at the ipsilateral shoulder joint (baseline and at the end intervention). Information from pain diaries documented and at the end satisfaction questionnaire (Brief).	Pain and pain relief examined through numerical rating scale (NRS) and verbal rating scale (VRS). Pain quality using the Short-Form McGill Pain Questionnaire (SF-MPQ). Both evaluations were performed at rest and painful movement. At the end, satisfaction questionnaire was used.	EORTC QLQ-C30 questionnaires related to nausea, vomiting and fatigue; global quality of life and five functional scales, together with a retrospective evaluation of drug-use during the five-day period.	Primary outcome of this study was the consumption of anaesthetics. Secondary end points were the time to spontaneous respiration, extubation time, eye-opening time, time to spontaneous movement, time to reorientation, and time to discharge from the operating room. After recovery room admission, the postoperative side effects, including incidence of respiratory depression, nausea, vomiting and pain, were also recorded at postoperative days 1, 2 and 3.

ALTENS: Acupuncture-like transcutaneous electrical nerve stimulation; EORTC QLQ-C30: Treatment and Research of Cancer, Quality-of-Life Questionnaire; G: Group; TEAS: Transcutaneous electric acupuncture stimulation TENS: *Transcutaneous electrical nerve stimulation;* TSE: Transcutaneous spinal electroanalgesia.

Treatment Effects

Gadsby *et al*., [16] observed that there was no significant difference between the groups and, if ALTENS had an effect on pain or nausea in palliative care, doubt was due to the low number of patients per group.

Robb *et al*., [17] observed that no significant differences existed between the two treatments and placebo using pain self-report alone, as well as no significant differences when patients had their anxiety, depression or shoulder range of movement evaluated. However, when examining pre- and post-treatment results, all three interventions improved worst and average pain scores when compared to baseline, but there was no evidence that there was superiority effect among interventions. Interestingly, the majority of patients reported long term effectiveness (at 3 and 12 months) and decided to continue using TENS, which happened in a lower percentage with the other interventions.

Furthermore, when examining the satisfaction questionnaire (Brief), TENS was considered significantly more effective than TSE or placebo. Overall, results from this study indicated that electrical stimulation is well tolerated in women with chronic pain related to breast cancer treatment and the majority of women improved as a result of the trial, but there is insufficient evidence to suggest that TENS is more effective than TSE or placebo.

Although Bennett *et al.*, [18] focused on TENS feasibility. The authors observed that change in bone pain levels on movement at 1 hour suggests that TENS has the potential to decrease pain on movement more than pain at rest, which is reflected by both pain-intensity and pain-relief scales. This is confirmed by the difference in pain relief on movement being greater than the differences in pain relief at rest. This might reflect the fact that mean pain intensity at rest was lower than during movement and therefore it’s easier to demonstrate change in scores on movement than at rest.

Liu *et al.*, [19] showed evidence that multipoint TEAS may be clinically effective as an adjunct to analgesia in intraoperative anesthesia and postoperative pain management, aiding in patient recovery. In this study, multipoint TEAS, both proximal and distal, combined with total intravenous anaesthesia

(TIVA), significantly decreased the use of non-intraoperative sufentanil. It also promoted an increased pain relief at the first PO day and better post-surgery recovery, without a significant increase on side effects.

Risk of Bias

Based on the following information, risk of bias from each study was assessed (Figure-2).

On the study by Bennet *et al*., [18], patients were randomized by a stratified permuted block method, to ensure balance between groups by age and gender. The investigator applying TENS was not blinded but it didn't participate on patient assessment. 10 out of 11 patients from placebo group correctly guessed group allocation. There was loss of data, but it was balanced between groups. All relevant outcomes were described. Regarding TENS application, there was no standardization of electrode placement, since it was dependent on localization of bone pain.

Gadsby *et al*., [16] randomized its subjects by sealed envelopes with a color code. Both subjects and investigators were blinded. Two out of five patients on the placebo groups did not complete the treatment protocol. Not all pre-established outcomes were reported. There was a small sample size (5 per group).

Liu *et al*., [19] used a computer-generated random number table for randomized subject allocation. The investigator applying the treatment was not blinded. Data was collected by a blinded investigator and data loss was balanced between groups. All described outcomes were reported. There was no standardization of treatment duration.

In the study by Robb *et al*., [17], patients were randomized by a computer-generated random number chart. Not enough information regarding subject allocation blinding was given. The investigator assessing the subjects was not blinded. Not enough information regarding data loss was reported. It was a crossover-type study, there was no standardization regarding electrode placement, treatment duration and pulse width.

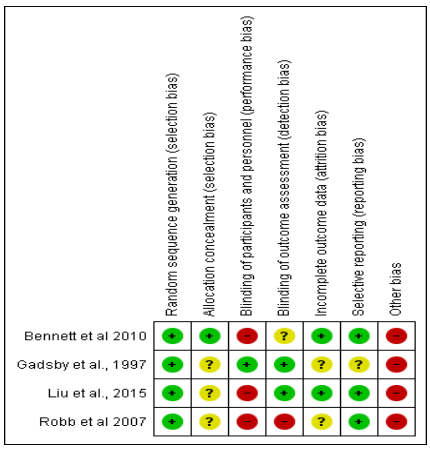

Fig-2: Methodological assessment of studies included in this review

DISCUSSION

The current evidence suggests that TENS can be useful for a variety of pain conditions such as fibromyalgia, neuropathic pain, neck pain, postoperative pain, labor pain, acute pain, low back pain and osteoarthritis pain [20-25]. But few clinical trials have been conducted to investigate TENS effects on cancer pain.

Although cancer is a disease with one of the highest incidences worldwide, pain can be caused by various etiological factors, such as progression of disease, treatment modalities (surgery, chemotherapy, or radiotherapy), musculoskeletal pain from inactivity, and cancer-related infections that result in neuropathic pain [26]. In this systematic review, only four articles were found, considering the inclusion and exclusion criteria, providing little conclusive data on the effectiveness of TENS in pain related to disease and preventing meta-analysis.

In the first study included in the systemic review performed by Gadsby *et al*., [16], the authors report that it is impossible to conclude on the effectiveness of TENS once it is a pilot study with such a small sample, but benefits in the quality of life and fatigue symptoms are suggested, justifying a deeper investigation on such effects.

Robb *et al*., [17] concluded that there is insufficient evidence to suggest that TENS is more effective than placebo for treatment-related pain in female cancer patients. Bennett *et al*., [18] suggests that TENS has the potential to decrease pain with movement more than pain at rest in patients with bone cancer. In all studies included in the systematic review, there were patients taking opioid analgesics or other pharmacological treatments for pain. This may be a factor for the lack of conclusive data on the use of TENS for cancer-related pain, because studies have shown that patients under use of opioids are less susceptible to benefit from TENS, due to a cross-tolerance effect [27, 28] which has been shown in rats that developed morphine tolerance and cross-tolerance to TENS [29, 30]. Furthermore clinically, it can be inferred that a treatment schedule of repeated daily TENS administration should be avoided due to the possibility of analgesic tolerance [31].

There are more than 100 distinct types and subtypes of cancer that can be found within specific organs with different painful conditions [1, 32]. But only two types of cancer were included in the articles of Robb *et al*., [17] and Bennett *et al*., [18] respectively, without specifying the etiology of pain or painful condition. These data demonstrate the need for more studies, that include other types of cancers, using a larger number of patients, with similar painful conditions and rigid control over the use of opioids, so that a more conclusive result can be reached.

Three other systematic reviews were previously performed investigating TENS and cancer. The first revision was published by Pan *et al.*, [33] included 4 articles for risk of bias analysis [16, 34-36]. Authors concluded that TENS may improve intractable pain in palliative care patients, but they used mainly non-randomized or case-series studies to support this conclusion.

The second and third systematic reviews on TENS and cancer were performed by [37] and [15]. The third review was an update of the second one. Therefore, the authors included 2 articles in the second review [16, 37] and added one article on the third review [18]. Both reviews concluded that the studies are inconclusive due to a lack of suitable randomized controlled trials. The present systematic review included all the articles from both reviews five years later, with the addition of one study, Liu *et al*., [19].

Although the current clinical evidence, due to the small number of studies and its low quality, is not sufficient to support the use of TENS for pain-reduction in cancer patients, evidence from basic research focused on mechanisms, suggest that those patients could benefit from this intervention. A variety of peripheral and central mechanisms of TENS have been described [13, 38, 39]. Most importantly, TENS acts through the release of endogenous opioids both peripherally and in the central nervous system [40-43]. Since the pharmacological option for cancer pain is opioid-based, there's support for TENS being effective in this population since it works on the same mechanisms.

However, since most cancer patients are under opioid-treatment, attention must be given to the possibility of cross-tolerance between the opioid drugs and TENS. High and low-frequency TENS activate different opioid receptors, delta (δ) and mu (μ), respectively [40-43]. This can be used for the treatment advantage, by applying high or low-frequency TENS depending on the drug receptor target, for example. By associating morphine (mu receptor agonist) and high frequency TENS (delta receptor activator), avoiding cross-tolerance and possibly, promoting a more effective analgesia due to the synergistic effect that occurs when delta and mu receptors are activated simultaneously [44, 45]. While evidence based practice is still poor to support the use of TENS in the clinical setting to treat cancer pain, a mechanism based approach should be emphasized to reason about what to prescribe to the cancer patients.

Although none of the included studies observed adverse effects with TENS application nor this outcome was investigated, important attention should be given to this possibility for this specific population. Studies have shown that low-frequency TENS can promote increases in blood flow at the site of application [46, 47], which brings concerns regarding the risk of metastasis for those patients. Further clinical studies should investigate this outcome and basic research should be focused on those mechanisms to bring evidence towards the safety of applying TENS in this population.

Uncertainty regarding those adverse effects from TENS prevented studies such as the one from Sun *et al*., [48] from including patients under high risk of tumor recurrence. So far, the only study investigating possible adverse effects was performed *in vitro*, were TENS influence on cell proliferation, invasion and migration was tested but no effect on those variables was observed [49]. Thus, assessing adverse effects is important, especially risk of metastasis since it is the number one cause of cancer mortality. This concern is related to the fact that cancer cells often secrete certain factors to increase tumor angiogenesis. These new blood vessels provide the necessary resources for rapid development of the tumor and also provide direct connections to the vascular system, facilitating the metastatic invasion in this system and dissemination throughout the body [50].

Further, based on the low number of studies investigating TENS on cancer pain and the methodological problems with the ones available, we recommend a set of criteria that should be taken into consideration in future studies investigating this subject.

Population: A rigorous selection criteria should be applied, excluding conditions that could produce confounding factors, such as previous opioid use, which can negatively influence TENS results due to a cross-tolerance effect. The underlying pain etiology might also be controlled, since cancer pain can have different origins and TENS treatment might have different results depending on the pain mechanisms at place.

Assessed outcomes: Future studies should use a more comprehensive patient evaluation, opposite to only assessing pain intensity at rest with a VAS scale. TENS has been shown to be more effective to reducing pain with movement [23, 51] and that outcome is more strongly associated with disability. Temporal summation and conditioned pain modulation are measures of central pain modulation and TENS is known to act through descending modulatory pathways [52, 53]. Other indirect outcomes such as analgesic consumption (can mask the differences between active and placebo TENS) and functional tests (can show increased function due to less pain) can be included to elucidate all different ways TENS can improve pain, that might not come through as a direct reduction of pain intensity. Finally, more clinically-relevant outcomes such as quality of life and satisfaction with treatment or patient's global perception should be included.

Treatment variables: Recent studies have been showing the importance of stimulation parameters such as frequency and intensity, for TENS overall effectiveness. It has been proposed that most of the negative results from TENS studies were possibly due to inadequate stimulation parameters. For example, a systematic review on the effects of TENS for postoperative pain showed an overall lack of effect of TENS when all studies were included in the analysis but the results were flipped to positive when only studies using adequate stimulation intensity were considered [20].

Besides stimulation intensity being a parameter that directly affects TENS effectiveness, different stimulation frequencies have been shown to act through different pathways, specifically, low-frequency TENS activates μ-opioid receptors and high-frequency TENS activates δ-opioid receptors [43, 54]. This is of importance when investigating cancer pain since the opioid medications often used by those patients might have positive or negative interactions with TENS depending on the target receptor of the medication and TENS frequency. So future studies should dedicate attention to the selected stimulation parameters to certify that they are adequate.

CONCLUSIONS

Based on the data of this study, we can conclude that there is insufficient evidence to demonstrate the efficacy of TENS in cancer-related pain. Further research with larger groups of patients, with similar features and randomized clinical trials are needed to better evaluate the feasibility of TENS in cancer-related pain.

Conflicts of Interest

The authors report no potential conflicts of interest

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