Meta-Analysis

Efficacy of Scrambler Therapy for Management of Chronic Pain: A Meta-Analysis of Randomized Controlled Trials

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Background: Although several randomized controlled trials (RCTs) have reported the efficacy of scrambler therapy (ST) for the management of chronic pain, those findings remain inconsistent.

Objectives: This meta-analysis aimed to investigate the efficacy of ST for the management of chronic pain.

Study Design: A meta-analysis of RCTs.

Methods: We searched core databases including PubMed, EMBASE, and the Cochrane library for RCTs in October 2021. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) for pain reduction were calculated using a random-effects model meta-analysis.

Results: Out of 348 studies, a total of 7 RCTs (n = 287 patients) that met the inclusion criteria were included in the final analysis. Overall, ST marginally decreased pain scores after the end of the treatment compared with the control group, with substantial heterogeneity (SMD, –0.85; 95% CI, –1.66 to –0.03; I^2 = 89.5%, n = 7). A subgroup meta-analysis found that the use of ST significantly reduced analgesic consumption compared to the control group (SMD, –0.54; 95% CI, –0.93 to –0.14; I^2 = 0.0%; n = 2). However, no significant efficacy was observed in the subgroup meta-analyses by methodological quality, type of diseases causing pain, and follow-up period.

Limitations: The included trials have a small sample size and low methodological quality.

Conclusions: ST seems to be effective in the management of patients with chronic pain. However, further, large RCTs are warranted to confirm our findings.

Key words: Scrambler therapy, Calmare therapy, chronic pain, meta-analysis, randomized controlled trials

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Chronic pain has emerged as a major health problem and has contributed to high health care costs and lost productivity (1-3). Some studies estimate that the prevalence of chronic pain is between 11% and 40% in the general population (4). Clinical trials and guidelines recommend a multimodal, interdisciplinary therapeutic approach that includes pharmacologic therapy, cognitive and behavioral modifications, rehabilitation therapy, and nonpharmacological interventions (5). Pharmacologic

therapy includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, musculoskeletal agents, opioids, or combinations of those medications (6). A mechanistic, reasonable approach to pharmacotherapy is an important component in the management of chronic pain (7). Opioids are commonly used for acute pain management. However, the evidence on the efficacy and risk-benefit profiles for the treatment of chronic pain is weak (8). The use of opioid drugs to treat pain is associated with serious adverse events such as sedation, respiratory depression, physical dependence, and addiction (9). Besides opioids, pharmacological agents involved in the treatment of chronic pain are associated with a risk of various systemic adverse events (10). Because of the substantial adverse events of the long-term multi-pharmacological therapies, there has been a growing interest in non-pharmacological approaches for sustained pain management (11).

Scrambler therapy (ST), which was introduced in 2003 by Giuseppe Marineo, is a noninvasive electrocutaneous stimulation therapy using 5 artificial neurons. It generates 16 different synthetic action potentials designed to convey "non-painful" information to the central nervous system (12,13). He hypothesized that ST works through the plasticity of the pain system under the control of information (12). In other words, the concept of ST is to modulate neuroplasticity to convert chronic pain signals into normal non-pain signals through scrambled electrical stimulation, not to suppress the noxious stimulation itself (12,14). Several clinical trials have been conducted to investigate the efficacy of ST in the treatment of chronic pain due to various diseases. In 2003, the inventor of ST introduced a small clinical trial investing its use in the management of chronic visceral cancer pain in 11 study patients (13). In this trial, all patients experienced a significant decrease in pain scores (13). Since then, various types of relatively small sample size studies such as randomized controlled trials (RCTs), prospective single-arm trials, clinical practice experiences, and retrospective studies have reported some beneficial effects of ST in various types of pain such as chemotherapy-induced peripheral neuropathy, chronic low back pain, post-herpetic neuralgia, and bone and visceral metastases (15,16). ST was approved by the US Food and Drug Administration (FDA) in 2009 for the symptomatic relief of acute and chronic pain, including acute post-surgical pain and post-traumatic pain, and has been widely used in clinical practice (17).

However, subsequent RCTs have reported inconsistent findings regarding the efficacy of ST in the management of pain (18-24). No meta-analysis has been published regarding the efficacy of the ST on chronic pain so far.

The current study aimed to evaluate the efficacy of ST for the management of chronic pain compared to the control groups such as placebos or other conventional treatments by using a meta-analysis of RCTs.

Methods

Scrambler Therapy

Theoretical Model

A well-known leading concept regarding the mechanism of pain perception and transmission is the gate control theory, which postulates a gate composed of excitatory and inhibitory synapses present in the dorsal horn of the spinal cord (25). It proposes that reinforcing input of A-beta fibers shuts the gate, thereby inhibiting transmission of nociceptive information that leads to pain perception (25). This theory serves as the scientific basis for the efficacy of transcutaneous electrical nerve stimulation (TENS) in pain reduction (26). Although TENS is widely used as an adjuvant to pharmacological or non-pharmacological pain management, the scientific data supporting its efficacy are still lacking and have not consistently demonstrated benefits, highlighting the need for new treatment options (27,28).

Figure 1 shows the theoretical model of ST. The principle of ST is based on Shannon's information theory, which is different from the gate control theory (12,29). Shannon's information theory proposes that "scrambled" artificial waveforms are assembled into dynamic strings of information (14,16,30) which are calibrated to synchronize surface receptors on C-fibers, converting endogenous pain information into synthetic "nonpain" information (12). Loss of a causal, linear relationship in the pain pathway may contribute to new, non-linear dynamical systems of chronic pain (12). This theoretical model provides a multidimensional understanding of chronic pain, making some phenomena that are difficult to explain with the gate control theory more intuitive and explainable (12).

Mechanism of Action

The functioning mechanism of ST is to control the neuroplasticity in chronic pain through informa-

tion control (12,16). It transmits coded information from painful nociceptors to "non-pain" signals by generating 256 types of dynamically assembled and modulated strings of information using 16 different synthetic action potentials (12,16). There are 4 main variables concerning the dynamically modifying algorithm that generates each new string: 1) 16 different synthetic action potentials, 2) packet frequency (43-52 Hz), 3) packet time duration (0.7-10 seconds), and 4) amplitude of modulation (18). The electrical stimulation intensity of ST ranges from 10 to 70 (18). The average amperage of ST does not exceed a maximum of 5.5 mA even at the highest "70" setting (18). Therefore, the average emission intensity is much lower than that of the conventional TENS (30-150mA) (12,18).

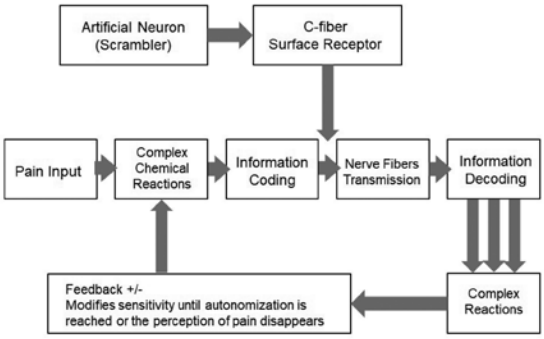

Fig. 1. *Theoretical model of Scrambler therapy. Adapted from Marineo G. Inside the Scrambler Therapy, a Noninvasive Treatment of Chronic Neuropathic and Cancer Pain (12).*

Device

The first industrialized original equipment manufacturer (OEM) version marketed in the US is the Scrambler Therapy® MC-5A, also known as its commercial brand name "Calmare" (Fig. 2). The second OEM version is the Scrambler Therapy® Technology MC-5A (12,31). In 4 of the 7 articles (18-20,24), the first or second OEM version of ST was used, whereas the remaining 3 articles (21-23) did not clarify which specific device of the ST was used.

Fig. 2. *Device for Scrambler therapy. The first industrialized original equipment manufacturer version device for Scrambler therapy, Scrambler Therapy® MC-5A, also known as its commercial brand name "Calmare."*

Eligibility Criteria

This meta-analysis was conducted based on the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (32,33). We included RCTs that met the following criteria: (1) Population - adult patients aged 18 years or older suffering from chronic pain lasting more than 3 months; (2) Intervention - ST using a standard Calmare device; (3) Comparisons - sham procedure, conventional medication, active comparator, or no treatment; (4) Outcome - pain assessment using a Numeric Rating Scale (NRS), a Visual Analog Scale (VAS), or a Brief Pain Inventory (BPI). If a study was duplicated, we selected the more comprehensive one.

Search Strategy

Two authors (YHJ and DHK) independently retrieved relevant studies from electronic databases (Cochrane Library, MEDLINE, EMBASE, CINAHL, and Scopus) in October 2021. The key words were: "Scrambler therapy" or "Calmare therapy." Because there were no Medical Subject Headings (MeSH) related to the following search terms, we used those free text words. The bibliographies of related articles were reviewed to identify additional publications in previous review articles and reference lists. There were no restrictions on the language of the publications.

Data Extraction and Quality Assessment

Two independent authors (YHJ and DHK) assessed the eligibility of studies, obtained data in a blinded manner, and assessed the methodological quality of the RCTs. If there were any discrepancies between the researchers, an agreement was reached through discussion and consultation with a third author (SKM). We extracted the name of the author, year of publication, sample size, the mean age of patients, disease type, outcome evaluation, follow-up interval, study type, and treatment type. We also investigated adverse event reports. The risk of bias was assessed based on the Cochrane risk of bias tool (34). Trials with a low risk of bias ≥ 5 items were considered as an overall low risk of bias study in this analysis.

Statistical Analysis

The primary endpoint was pain score after the treatment with ST. The time and frequency for the post-treatment pain assessments and the intervals between the baseline pain assessment and the post-treatment pain assessments are different across the studies. Thus, in the main analysis, we used the pain score for the post-treatment closest to the final treatment date in each study: prior to or immediately after the final treatment in 5 studies, a week after the final treatment in a study, and a month after the final treatment in a study. The secondary endpoints were analgesic consumption and adverse events.

In order to calculate a pooled standardized mean difference (SMD) with a corresponding 95% confidence interval (CI), we used an SMD with a 95% CI, which is calculated by subtracting the mean value in the control group from the mean value in the intervention group in each trial. Median (interquartile range or range) values were converted to mean (standard deviation) values. Because individual trials were performed in the different populations, we used a random-effects model meta-analysis based on the DerSimonian and Laird method (34,35). Study-wide heterogeneity was evaluated using Higgins I^2 to measure the overall variance (36). An I^2 value exceeding 50% was considered as substantial heterogeneity (36). The statistical analyses were performed using Stata/MP version 17.0 software package (StataCorp, College Station, TX).

Results

Study Selection

A flow chart of the selection process for this study is shown in Fig. 3. A total of 348 articles were identified

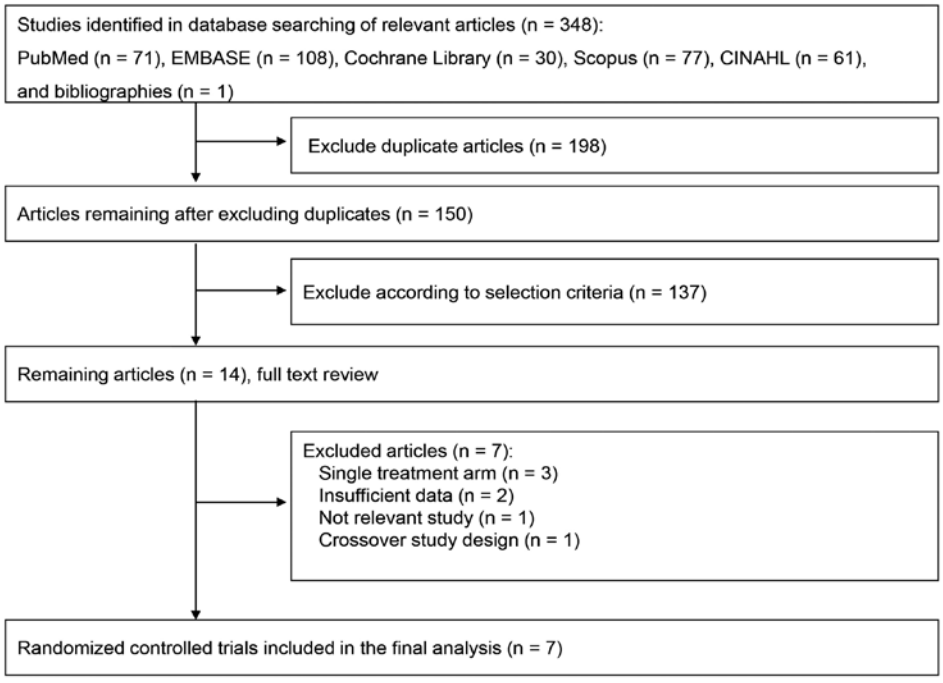

Fig. 3. *Flow diagram for identification of relevant studies.*

through electronic searches of 4 databases and manual searches of relevant bibliographies. After removing 198 duplicated articles, the 2 independent authors assessed the eligibility of all articles based on their titles and abstracts, and additional 137 articles that did not meet the predefined selection criteria were excluded. Fourteen full-text articles were then reviewed for the final selection. Seven articles were excluded for the following reasons: single treatment arm (n = 3), insufficient data (n = 2), not relevant study (n = 1), and crossover study design (n = 1). The remaining 7 RCTs were included in the final analysis (18-24).

Study Characteristics

Table 1 shows the general characteristics of the RCTs included in the final analysis. The publication years were between 2012 and 2020; a total of 287 patients (142 in the intervention group and 145 in the control group) were

Table 1. *Characteristics of trials included in the final analysis (n = 7).*

	Source	Number of patients (S/C)	Pain condition	Scrambler therapy group	Control group	Pain assessment	Follow-up	Main findings
1	Marineo 2012 (18)	26/26	Postsurgical neuropathic pain, PHN, and SS	45 minutes for 10 days up to maximal tolerable intensity (70 U)	Conventional medical treatment	VAS	1 month, 2 month, and 3 months	Significant reduction in pain score at 1 month from 8.0 to 0.7 in the Scrambler therapy group, compared with 8.1 to 5.8 in the control group ($P < 0.0001$)
2	Campbell 2013 (19)	5/5	CIPN	50 minutes for 10 days	Sham	Verbal-NRS	10 days	No significant difference in changes in pain score change between both groups ($P = 0.57$)
3	Starkweather 2015 (20)	15/15	Persistent nonspecific low back pain	30 minutes for 10 days up to maximal tolerable intensity (70 U)	Sham: one set of electrodes placed above painful dermatome, under nontherapeutic threshold	BPI-SF	1 week and 3 weeks after the end of the treatment	Significant reduction in worst pain score at 1 week from 5.40 to 4.34 in the Scrambler therapy group, compared with 4.98 to 5.76 in the sham group ($P = 0.01$).
4	Kashyap 2020 (21)	40/40	Cancer pain	40 minutes for 10 days up to maximal tolerable intensity	Conventional medical treatment	NRS	1 week after the end of the treatment	Significant difference in pain score reduction between the Scrambler therapy group (6.19) and the control group (3.1) at 1 week after the end of the treatment ($P < 0.001$)
5	Loprinzi 2020 (22)	15/19	CIPN	30 minutes for 10 days up to maximal tolerable intensity	TENS	NAS	Daily for 2 weeks and then weekly for 8 additional weeks	At least a 50% documented improvement during the 2 treatment weeks in the Scrambler therapy group, compared with the TENS group
6	Nayback-Beebe 2020 (23)	25/23	PHN, CIPN, SS, and postsurgical neuropathic pain	30 minutes for 10 days,	Sham: nontherapeutic threshold, placing leads outside painful dermatomes	NRS	Post-treatment (after last treatment session) and 4 weeks post-treatment)	No significant difference in changes in pain score reduction at 4 weeks post-treatment between both groups ($P = 0.494$)
7	Smith 2020 (24)	16/17	CIPN	30 minutes on 10 days up to maximal tolerable intensity	Sham: placed in an "X" across the L2-5 or C5-8 region	BPI-CIPN	Days 10, 28, 60, and 90	No significant difference in pain score reduction on day 10 ($P = 0.296$)

Abbreviations: S, Scrambler therapy group; C, control group; PHN, post-herpetic neuralgia; CIPN, chemotherapy induced peripheral neuropathy; SS, spinal stenosis; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale; NRS, numeric rating scale; BPI-SF, Brief Pain Inventory – Short Form; NAS, numerical analog scale

included in this meta-analysis. Pain conditions were chemotherapy-induced peripheral neuropathy (CIPN) in 4 trials (19,22-24), postsurgical neuropathic pain in 2 trials (18,23), post-herpetic neuralgia (18,23), pain due to spinal stenosis (18,23), cancer pain (21) in one trial, and persistent nonspecific low back pain in one trial (20). Treatment time and period were approximately 30 to 50 minutes per session over 10 working days. The control groups were conventional medical treatment, sham treatment, and TENS. The pain was assessed by using a VAS, NRS, BPI-short form (SF), NAS, and BPI-CIPN. Follow-up periods ranged between 10 days and 3 months from baseline. In the main findings, 3 trials showed no significant difference in changes in pain score (19,23,24), whereas 3 trials showed a significant reduction in pain score between the ST group and the control group (18,20,21). The remaining one did not report a statistical significance (22).

Methodological Quality

In the assessment of the methodological quality score based on the Cochrane risk-of-bias tool, 2 trials demonstrating the low risk of bias ≥ 5 items were categorized as having high quality (20,24), while the remaining 5 low-quality trials had a low risk of bias < 5 items (18,19,21-23) (Table 2). The included trials were generally of low quality, mostly related to lack of blinding. Due to the small number of studies (< 10), we could not rule out publication bias by performing funnel plots (37).

Efficacy of Scrambler Therapy on Pain Relief

In the random-effects model meta-analysis of 7 RCTs, ST marginally decreased pain after the end of the treatment compared with the control group (SMD, –0.85; 95% CI, –1.66 to –0.03; I^2 = 89.5%; Fig. 4). All the included studies reported different follow-up periods ranging from immediately to 3 months after the treatment.

Subgroup Meta-Analysis

Tables 3 shows the efficacy of ST for the management of chronic pain in the random-effects model subgroup meta-analysis by various factors. Subgroup meta-analysis showed that the use of ST significantly reduced analgesic consumption after the intervention compared to the control group (SMD, –0.54; 95% CI, –0.93 to –0.14; I^2 = 0.0%; n = 2). In the subgroup meta-analysis by type of control group, ST showed superior effects in relieving chronic pain than conventional medical treatment (SMD, –2.28; 95% CI, –2.80 to –1.76; I^2 = 24.5%; n = 2), whereas there was no significant difference, compared to the sham group (SMD, –0.22; 95% CI, –0.64 to 0.19; I^2 = 19.7%; n = 4). No significant association was observed in the remaining subgroup meta-analyses by methodological quality, type of diseases causing pain (CIPN or noncancerous origin), and follow-up period.

Adverse Events

Five out of 7 trials investigated the adverse events of ST (18-22). Among them, 2 (19,22) reported 2 adverse events: small bowel obstruction in a patient in the sham group (19) and minor ecchymosis at the site of the electrode placement in a patient (22). No severe adverse event was reported from all the included studies.

Table 2. *Summary of risk of bias assessment for the included trials (n = 7).*

Source	Random Sequence Generation	Allocation Concealment	Blinding of Patients, and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	No. of Low Risk of Bias
Marineo 2012 (18)	Low	High	High	High	Low	Low	Unclear	3
Campbell 2013 (19)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	0
Starkweather 2015 (20)	Low	Low	Low	Unclear	Low	Low	Unclear	5
Kashyap 2020 (21)	Low	Low	High	High	Unclear	Low	Low	4
Loprinzi 2020 (22)	Low	Low	High	High	Unclear	Low	Low	4
Nayback 2020 (23)	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	0
Smith 2020 (24)	Low	Low	Unclear	Low	Unclear	Low	Low	5

[a]Based on the Cochrane Risk of Bias Tool.

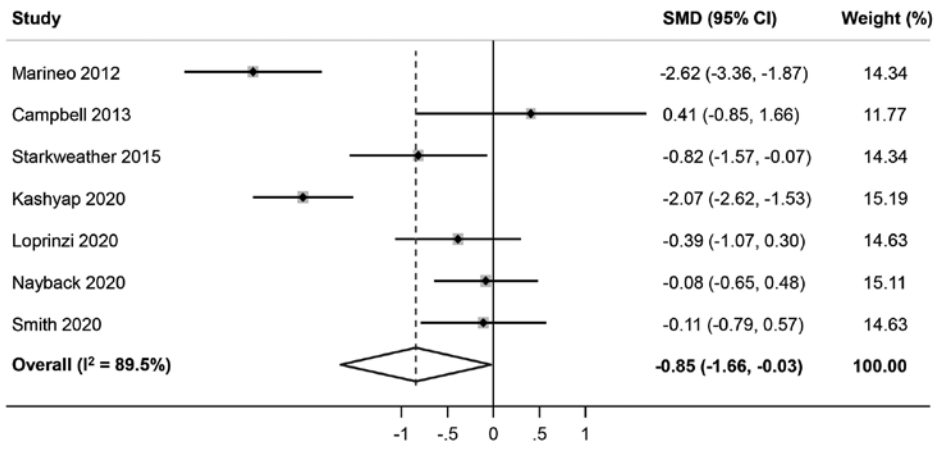

Fig. 4. *Use of Scrambler therapy and change of pain score based on the initial evaluation after the end of the treatment in a random-effects meta-analysis of randomized controlled trials (n = 7).*
SMD, standardized mean difference; CI, confidence interval.

Table 3. *Efficacy of scrambler therapy for management of chronic pain in random-effects model subgroup meta-analyses by various factors.*

Factor	Number of studies	Number of patients	SMD (95% CI)	Heterogeneity, I^2
All**	7	287	-0.85 (-1.66 -0.03)	89.5%
Analgesics dose*	2 (21,23)	103	-0.54 (-0.93, -0.14)	0.0%
Methodological quality				
High-quality (Low risk of bias in ≥ 5 items) Post-immediate follow-up 1 month follow-up	 2 (20,24) 2 (20,24)	 63 63	 -0.45 (-1.14, 0.24) -0.45 (-2.01, 1.12)	 46.6% 88.8%
Low-quality (Low risk of bias in ≤ 4 items)	5 (18,19,21,22,23)	224	-0.99 (-2.10, 0.11)	92.0%
Type of diseases				
CIPN	3 (19,22,24)	77	-0.16 (-0.62, 0.29)	0.0%
Non-cancer pain	2 (18,20)	82	-1.72 (-3.48, 0.04)	91.0%
Follow-up period				
1 month	3 (18,23,24)	133	-0.69 (-2.45, 1.06)	95.2%
2 months	2 (18,24)	85	-0.93 (-2.72, 0.87)	93.1%
3 months	2 (18,24)	85	-0.60 (-2.24, 1.04)	92.2%
Type of control group				
Sham	4 (19,20,23,24)	121	-0.22 (-0.64, 0.19)	19.7%
Conventional medical treatment*	2 (18,21)	132	-2.28 (-2.80, -1.76)	24.5%

*Statistically significant, **Marginally significant. SMD, standardized mean difference; CIPN, chemotherapy-induced peripheral neuropathy; RR, relative risk; CI, confidence interval

Discussion

In the current meta-analysis of 7 RCTs, ST showed marginally significant reductions in pain scores and significant reductions in analgesic consumption scores compared to the control group. The incidence of adverse events in the ST group was not higher than that in the control group.

However, we found that there are a lot of limitations in investigating the efficacy of ST in pain manage-

ment. First, most RCTs showed a high risk of bias in the assessment of methodological quality, which is due to a limitation for blinding of study patients and research personnel. The appropriate use of operator-dependent ST does not allow complete double-blind trial designs (31). When conducting ST, the optimal electrode position and stimulation intensity should be determined through interaction with a patient, thereby aiming for complete pain relief (31). Attempting a complete double-blind clinical trial would automatically distort the standard treatment protocol prominently (31).

Second, there was substantial heterogeneity in the main analysis. There were several reasons which may account for the heterogeneity between studies: different pain assessment scale, pain condition, sample size, follow-up period, type of control group, and procedural protocol across trials.

Third, specific diseases causing pain were not well documented. All the included trials (18-24) did not present a reliable, standardized criteria for the diagnosis of a specific disease that the study patients had.

Fourth, there were lots of differences in the placement and number of electrodes between the ST group and the sham group. For example, in Starkweather et al's (20) study, the placement and number of electrodes were different between the ST and sham groups, and the settings involved a nontherapeutic range in the sham group. In Nayback-Beebe et al's (23) study, leads were placed outside the affected dermatome and at the nontherapeutic threshold. Smith et al's (24) study used the different electrode arrangement between the ST group and the sham group and the same maximum threshold.

Fifth, procedural problems were also observed in several RCTs. In general, the electrodes should not be applied directly to the site of pain but to the dermatome above and below the site (18). After the primary pain site and its borders have been identified, the electrodes placement should surround the proximal to the distal border of the skin at the pain site (38). It is not recommended to place the electrodes at the site of numbness or sensory changes (24). Neural pathways that cause numbness or sensory changes due to structural or functional impairments may not effectively transmit or even degrade the synthetic "nonpain" information (12).

Sixth, given that the effect of ST is practice-dependent and improves with follow-up training, there is inevitably a difference in the skill levels of practitioners performing the ST, which further affects the results of the trial (16,39,40).

Lastly, we included only 7 studies involving 287 patients in the main analysis. The number of study patients in each trial ranged between 10 and 80, which is considered very small.

Conclusions

To the best of our knowledge, this is the first meta-analysis to evaluate the efficacy of ST for the management of chronic pain. In summary, we found that ST is effective in reducing pain in the short term in adults with chronic pain. However, there are several important limitations to prove its efficacy due to the small sample size of the included trials (10 to 80 study patients), low methodological quality, inappropriate methods, and use of sham procedure. Further large-scale trials with at least several hundreds of study patients are warranted to confirm our findings on the efficacy of the ST in the management of chronic pain.

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