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REVIEW ARTICLE

Meta-analysis of transcutaneous electrical nerve stimulation for relief of spinal pain

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Abstract

We conducted a systematic review and meta-analysis analysing the existing data on transcutaneous electrical nerve stimulation (TENS) or interferential current (IFC) for chronic low back pain (CLBP) and/or neck pain (CNP) taking into account intensity and timing of stimulation, examining pain, function and disability. Seven electronic databases were searched for TENS or IFC treatment in non-specific CLBP or CNP. Four reviewers independently selected randomized controlled trials (RCTs) of TENS or IFC intervention in adult individuals with non-specific CLBP or CNP. Primary outcomes were for self-reported pain intensity and back-specific disability. Two reviewers performed quality assessment, and two reviewers extracted data using a standardized form. Nine RCTs were selected (eight CLBP; one CNP), and seven studies with complete data sets were included for meta-analysis (655 participants). For CLBP, meta-analysis shows TENS/IFC intervention, independent of time of assessment, was significantly different from placebo/control ($p < 0.02$). TENS/IFC intervention was better than placebo/control, during therapy ($p = 0.02$), but not immediately after therapy ($p = 0.08$), or 1–3 months after therapy ($p = 0.99$). Analysis for adequate stimulation parameters was not significantly different, and there was no effect on disability. This systematic review provides inconclusive evidence of TENS benefits in low back pain patients because the quality of the studies was low, and adequate parameters and timing of assessment were not uniformly used or reported. Without additional high-quality clinical trials using sufficient sample sizes and adequate parameters and outcome assessments, the outcomes of this review are likely to remain unchanged.

Significance: These data highlight the need for additional high-quality RCTs to examine the effects of TENS in CLBP. Trials should consider intensity of stimulation, timing of outcome assessment and assessment of pain, disability and function.

1. Introduction

Transcutaneous electrical nerve stimulation (TENS) is an electrotherapeutic procedure used for pain control that was first introduced to the medical community by Wall and Sweet in 1967 (Wall and Sweet, 1967). In 2012, the Center for Medicare Services rendered a decision stating as follows: 'TENS is not reasonable and necessary for the treatment of

CLBP [chronic low back pain]' (cms.gov). Systematic reviews similarly conclude that TENS is ineffective or inconclusive for a variety of painful conditions (Khadilkar et al., 2008; Nnoaham and Kumbang, 2008; Dowswell et al., 2009; Kroeling et al., 2009; Rutjes et al., 2009; Walsh et al., 2009; Hurlow et al., 2012). On the other hand, Jauregui et al. (2016) concluded in their systematic review that the treatment of chronic low back pain with TENS demonstrated significant pain reduction in patients who were treated for less than 5 weeks. Prior studies, however, have not considered important aspects of TENS treatment, namely intensity of stimulation and timing of assessment. We have previously suggested several factors may contribute to the equivocal findings in the literature on TENS effectiveness. These factors include dosing of TENS, timing of assessment, the population assessed and type of outcome (Sluka et al., 2013). Similarly, Bennett and colleagues describe significant biases in study design and implementation fidelity – the most prevalent being suboptimal dosing of TENS and inappropriate outcome assessments (Bennett et al., 2011). Notably, these factors are often not considered when designing clinical trials or systematic reviews.

Dosing of TENS using intensity modulation is critically important to obtain a positive effect (Bjordal et al., 2003; Rakel and Frantz, 2003; Rakel et al., 2010; Moran et al., 2011). TENS delivered at a strong but comfortable intensity provides a significant analgesic effect while TENS delivered at or below sensory threshold is ineffective (Bjordal et al., 2003; Aarskog et al., 2007; Rakel et al., 2010). Analysis in systematic reviews that consider dosing show high intensities are associated with significant reductions in post-operative pain, osteoarthritis pain and acute pain (Rakel and Frantz, 2003; Bjordal et al., 2007; Johnson et al., 2015). In fact, if intensities are below an adequate dose, TENS is ineffective (Bjordal et al., 2003, 2007). Timing of outcome assessment is also critically important to determine the peak effect of any intervention. For TENS, peak effects occur when the unit is on or immediately after it is turned off in (Melzack et al., 1983; Marchand et al., 1993; Leonard et al., 2010; Vance et al., 2012).

Also, critical to the evaluation of TENS, effectiveness is the patient population studied and the outcomes measured. TENS produces its effects by increasing endogenous opioid release and reducing central excitability (Vance et al., 2014). Thus, patients with deficits in endogenous inhibition or enhanced central excitability are more likely to respond to TENS, based on the underlying mechanisms. Further, while TENS may have an effect on resting pain in some populations (Marchand et al., 1993; Facci et al., 2011), it appears to be more effective for reducing pain during movement and hyperalgesia in other conditions (Cheing et al., 2003; Rakel and Frantz, 2003; Law and Cheing, 2004; Law et al., 2004; Vance et al., 2014). It follows that if pain is reduced, function and disability will be improved. However, studies that examined function and disability using surveys and performance-based tests have reported mixed results, perhaps because they primarily measured resting pain (Cheing et al., 2002, 2003; Buchmuller et al., 2012).

The purpose of this systematic review was to analyse the existing data on the use of TENS in a population expected to have enhanced excitability and reduced inhibition, non-specific chronic low back and neck pain patients, taking into account in the analysis the intensity and timing of stimulation, and examining pain and disability outcomes.

2. Methods

This study adhered to the recommendations proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions (Moher et al., 2009; Higgins et al., 2011) with the exception of pain outcome reporting recommended as greater than 30% or 50% pain relief. These pain outcomes were not found in the existing literature. The systematic review has been registered at PROSPERO, CRD42016029849 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016029849).

2.1 Selection criteria

2.1.1 Types of studies

The systematic review included randomized controlled trials (RCTs) of TENS or interferential current (IFC) application in individuals with non-specific chronic low back pain (CLBP) or chronic neck pain (CNP). All studies were randomized controlled trials with parallel designs. No sample size criteria were established for inclusion of RCTs.

2.1.2 Types of participants

Adult participants (age 18 or older) with a diagnosis of non-specific CLBP and/or CNP were considered. CLBP was defined as low back pain that has persisted for 3 months or longer, does not have

radicular signs and is not the manifestation of a clearly defined and generally recognizable primary disease entity such as cancer, multiple sclerosis and rheumatoid arthritis (www.cms.gov). CNP was defined as nonradicular pain located in the anatomical region of the neck that has persisted for 3 months or longer, including work-related neck pain, myofascial neck pain and upper trapezius myalgia. The pain had to be non-specific, meaning that no specific cause was detectable, such as infection, neoplasms, metastasis, osteoporosis, rheumatoid arthritis, fractures or inflammatory processes. Trials were excluded if they reported subjects with diagnoses of acute (pain duration of 6 weeks or less) or subacute (pain duration of 6–12 weeks) back or neck pain. In addition, trials investigating subjects with a medical diagnosis, signs, or symptoms of radiculopathy, a previous history of back surgery, pain conditions other than CLBP or CNP and mixed pain conditions were excluded of this study.

2.1.3 Types of interventions

RCTs that determine the effectiveness of standard TENS or IFC therapies were considered in this systematic review and meta-analysis. Comparison groups included in this review were 'sham' TENS (placebo group) and/or standard care. An acceptable 'sham' TENS placebo group was defined as a group having a TENS or IFC device modified so that no electrical current passed to the skin surface electrodes. We collected information specifically related to TENS and IFC device parameters, stimulation settings, application method, treatment schedule, concurrent interventions and adverse effects. Trials in which the active treatment groups received TENS or IFC plus other treatment, or another electrical stimulation treatment such as Percutaneous Electrical Stimulation (PENS), Neuromuscular Electrical Stimulation (NMES), Microcurrent, Galvanic, Diadynamic, Pulsed High Voltage Current (HVPC), or any other form of invasive current, were not accepted for this study.

2.1.4 Types of outcome measures

The primary outcome measures included the following: pain intensity (typically measured using a visual analogue scale (VAS) and back-specific function (measured using Oswestry Disability Index (ODI) or other specific function scale). Secondary outcome measures considered for inclusion were general health (Short-Form Health Survey (SF-36)), patient satisfaction (Patient Satisfaction Survey) and adverse effects. The timing of assessment of all outcomes (e.g. during, immediately after, 1 week after, 2–4 weeks after, 2–3 month after) was also considered.

2.2 Search strategy

Bibliographical database search strategies were developed with the assistance of a health sciences librarian with expertise in searching for systematic reviews. Comprehensive search strategies, including both index and keyword methods, were devised for the following databases: PubMed (including MEDLINE), CINAHL (EBSCO platform), Embase (Elsevier platform), Physiotherapy Evidence Database (PEDro) and Cochrane Central Register of Controlled Trials (Wiley platform). No preset database filters were utilized, in an effort to maximize sensitivity. To minimize bias of results, language filters were also not used, and a plan for translation of appropriate papers was established. Search filters designed for systematic review searching to identify clinical trials were added to the PubMed, CINAHL and Embase strategies (Haynes et al., 2005; Wong et al., 2006). The PubMed strategy, which can be viewed in Table 1, was then adapted for the other listed databases. Finally, several Google Scholar searches were conducted to supplement the database searches. The described searches were initially conducted during November/December 2014, and then updated prior to the final analysis to identify papers published during the screening process. In addition, manual searching of reference lists of retrieved studies, conference proceedings, the literature reviews and textbooks were conducted to capture records from non-traditional sources. No limits were applied for publication date.

2.3 Study selection and data extraction

Four reviewers (L.O., R.L., E.M., D.D.) independently selected the trials to be considered in the review by screening the titles, abstracts and full text sequentially, according to the eligibility criteria prespecified. These reviewers were blinded to the journal and authors during the title screening process, but not during the abstract and full-text screening process. A fifth reviewer (K.S.) was consulted to help resolve differences. In the data extraction phase, two reviewers (L.O., R.L.) extracted all data and recorded in a standardized form. The data extraction form included study design, population characteristics, control and treatment interventions, therapeutic dose, treatment schedule, electrodes details, outcome measures used and follow-up period. Differences in

Table 1 The PubMed search strategy used to identify potential manuscripts.

'Transcutaneous Electric Nerve Stimulation'[Mesh] OR 'Electric Stimulation Therapy'[Mesh] OR 'Electric Stimulation'[Mesh] OR electric stimulation [Text Word] OR electrical stimulation[Text Word] OR electrostimulation[Text Word] OR TENS[Text Word] OR nerve stimulation[Text Word] OR electrotherapy[Text Word] OR interferential current[Text Word] OR electroanalgesia[Text Word]
AND
'Back Pain'[Mesh] OR 'Neck Pain'[Mesh] OR back pain[Text Word] OR back pains[Text Word] OR back ache[Text Word] OR backache[Text Word] OR back aches[Text Word] OR backaches[Text Word] OR lumbargo[Text Word] OR LBP[Text Word] OR lumbar pain[Text Word] OR sacral pain[Text Word] OR lumbosacral pain[Text Word] OR sacroiliac pain[Text Word] OR neck pain[Text Word] OR neck pains[Text Word] OR neckache[Text Word] OR neckaches[Text Word] OR neck ache[Text Word] OR neck aches[Text Word] OR cervicalgia[Text Word] OR cervical pain[Text Word] OR cervical pains[Text Word] OR cervical ache[Text Word] OR cervical aches[Text Word]
AND
clinical[tiab] AND trial[tiab] OR 'clinical trials as topic'[mesh] OR 'clinical trial'[pt] OR random*[tiab] OR 'random allocation'[mesh] OR 'therapeutic use'[sh]
NOT
'Animals'[Mesh] NOT ('Animals'[Mesh] AND 'Humans'[Mesh)

data extraction were resolved by referring back to the original article and establishing consensus. A third reviewer (K.S.) was consulted to help resolve differences.

2.4 Quality assessment and risk of bias

Two investigators performed the methodological quality assessment independently, applying the Cochrane Collaborations tool (Higgins et al., 2011) to judge the risk of bias of the studies. Six domains of bias were evaluated in this review: selection bias (randomization sequence generation, allocation concealment), performance bias (blinding of participants), detection bias (blinding of outcome assessor), attrition bias (incomplete outcome data), reporting bias (source of funding bias), and other bias (sample size, stimulation parameters). We designated sample size based on the number of subjects per arm as suggested by Bennett, and described as follows: high risk of bias <50 patients per arm, moderate risk of bias 50 to 199 patients per arm and low risk of bias ≥200 patients per arm. Stimulation parameters were deemed appropriate if the intensity was strong but comfortable or greater, frequency and pulse durations were within standard ranges (1–150 Hz frequency; 50–350 μs pulse duration) and electrodes surrounded the painful area (placed over the lumbar spinal musculature). For each study, each item was rated according to three categories: low risk, high risk and unclear risk (studies without a clear description of these features). Then, the overall risk of bias for all domains of each study was rated as low, high or unclear.

2.5 Data analysis

The meta-analysis was conducted using the Review Manager statistical software (RevMan version 5.3). We extracted the sample size, means and standard deviations for each variable. When the trial reported only standard errors, they were converted to standard deviations. When necessary, the mean scores and standard deviations were estimated from graphs. For the Deyo study (Deyo et al., 1990), we calculated standard deviation from confidence intervals provided by for the difference scores. When the same study had two or more assessments in the same group, we used the assessment with the greatest effect.

Random-effects meta-analysis was performed after we predicted the effects sizes would differ across studies (Iverson et al., 2009). Statistical heterogeneity was detected using a Q-test (x^2) and reported as I^2-statistic, in that values were considered indicative of low heterogeneity if <25%, moderate <50% and high >50%. Because of the absence of data for other outcomes (health-related quality of life, satisfaction with treatment, and adverse effects), we performed analyses only for the primary outcomes: pain intensity and back-specific function. The outcome measures of the included studies were 10 cm or 100 mm VAS or 0- to 10-point numerical pain rating scale (NPRS) for assessment of self-reported pain, and the 100-point Oswestry Disability index for assessment of back-specific function (Mousavi et al., 2006). Pain scores deviating from a 10-point scale were transformed linearly to a 0–10 point scale (Herr et al., 2004). Considering pain intensity and back function as continuous variables, we calculated the weighted mean differences (WMDs) and the corresponding 95% confidence intervals (95% CIs) based on the postintervention means of treatment and control groups. Based on current research, an improvement in pain intensity of 2-points (0 to 10 points) was considered clinically significant (Salaffi et al., 2004).

For back-specific function, a 10-point improvement on the Oswestry Disability index (Ostelo et al., 2008) was considered clinically important.

3. Results

3.1 Study search

Fig. 1 presents a flow diagram summarizing the study selection process. The initial search identified a total of 4186 references to potential studies from PubMed, Embase, Cochrane Controlled Trials Register, CINAHL, and PEDro, 478 from Google Scholar and 140 from hand searching. Following removal of duplicate, screening of titles and abstracts identified 125 potential studies. After a detailed review of full text of retrieved studies, nine articles met the inclusion criteria and seven of these were eligible for inclusion in the meta-analysis. The most prevalent reasons for exclusion were invalid reference, not a randomized clinical trial, the absence of control group, and pain condition other than chronic.

3.2 Study characteristics

The main characteristics of the included studies are described in Table 2. All nine articles selected for the review were randomized clinical trials in English.

3.2.1 Participants

Altogether, 655 participants were included in the reviewed RCTs, ranging from 24 subjects per sample to 150. In relation to sample size, all studies had fewer than 50 patients per arm. Most studies were performed in individuals with chronic low back pain ($N = 575$); only one trial was performed in those with chronic neck pain ($N = 80$) (Sahin et al., 2011). Participants ranged in age from 18 to 60 in most of the studies; Alizadeh et al. had a young adult (mean age 22 years old) sample (Alizadeh and Ahmadizad, 2009), and Itoh et al. study had an older adult (61–81 years old) sample (Itoh et al., 2009). In general, there was a prevalence of female subjects in the sample.

3.2.2 Intervention

In seven studies, TENS was the only intervention (Deyo et al., 1990; Marchand et al., 1993; Cheing and Hui-Chan, 1999; Topuz et al., 2004; Kofotolis et al., 2008; Alizadeh and Ahmadizad, 2009; Sahin et al., 2011). Facci et al. study examined both TENS and interferential current interventions (Facci et al., 2011), and Itoh et al. reported the intervention as TENS but was actually interferential current (Itoh et al., 2009) (described as premixed amplitude-modulated frequency of 122 Hz (beat frequency) generated by two medium frequency sinusoidal waves of 4.0 and 4.122 kHz (feed frequency)). Six studies compared TENS with placebo-TENS (Deyo et al., 1990; Marchand et al., 1993; Cheing and Hui-Chan, 1999; Topuz et al., 2004; Kofotolis et al., 2008; Sahin et al., 2011). Alizadeh et al., and Facci et al., compared TENS with a control group that received prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) or received written instructions about vertebral column care, respectively (Alizadeh and Ahmadizad, 2009; Facci et al., 2011). And one, Itoh et al., reported on IFC intervention compared to a control group using topical poultice containing methylsalicylic acid (Itoh et al., 2009). In the trials that evaluated IFC, none of them used a placebo-IFC as a comparison group.

There was considerable variation between studies in treatment schedule and stimulation parameters (frequency, pulse duration, etc.). Table 3 presents the description of stimulation parameters of included studies. For the treatment schedule, most studies had a duration of treatment lasting between 2 and 5 weeks, performed treatments 2 to 5 days per week, with individual treatments ranging from 15 to 60 min. Cheing et al., reported a single 60-min session of treatment (1 day during 1 week) (Cheing and Hui-Chan, 1999). Deyo et al. reported a daily session of 135 min (3 repetitions of 45 min) but did not describe how many days a week (Deyo et al., 1990). All trials described complete information about frequency, pulse duration and intensity of the current, except Alizadeh et al. (Alizadeh and Ahmadizad, 2009) Two studies reported using conventional/high-frequency TENS (C-TENS; 80–100 Hz; Marchand et al., 1993; Cheing and Hui-Chan, 1999); two studies reported using acupuncture-like/low-frequency TENS (A-TENS; 2–20 Hz; Kofotolis et al., 2008; Facci et al., 2011), and three studies had both high and low-frequency TENS groups (Deyo et al., 1990; Topuz et al., 2004; Sahin et al., 2011). Alizadeh et al. used a frequency modulating between low and high frequency (10–70 Hz; Alizadeh and Ahmadizad, 2009). For studies with interferential current, carrier frequency and AMF were reported (Itoh et al., 2009; Facci et al., 2011). Two studies involved different groups for high-frequency and low-frequency TENS (Topuz et al., 2004; Sahin et al., 2011), while Deyo et al. recruited subjects to receive high frequency during the first 2 weeks and low or

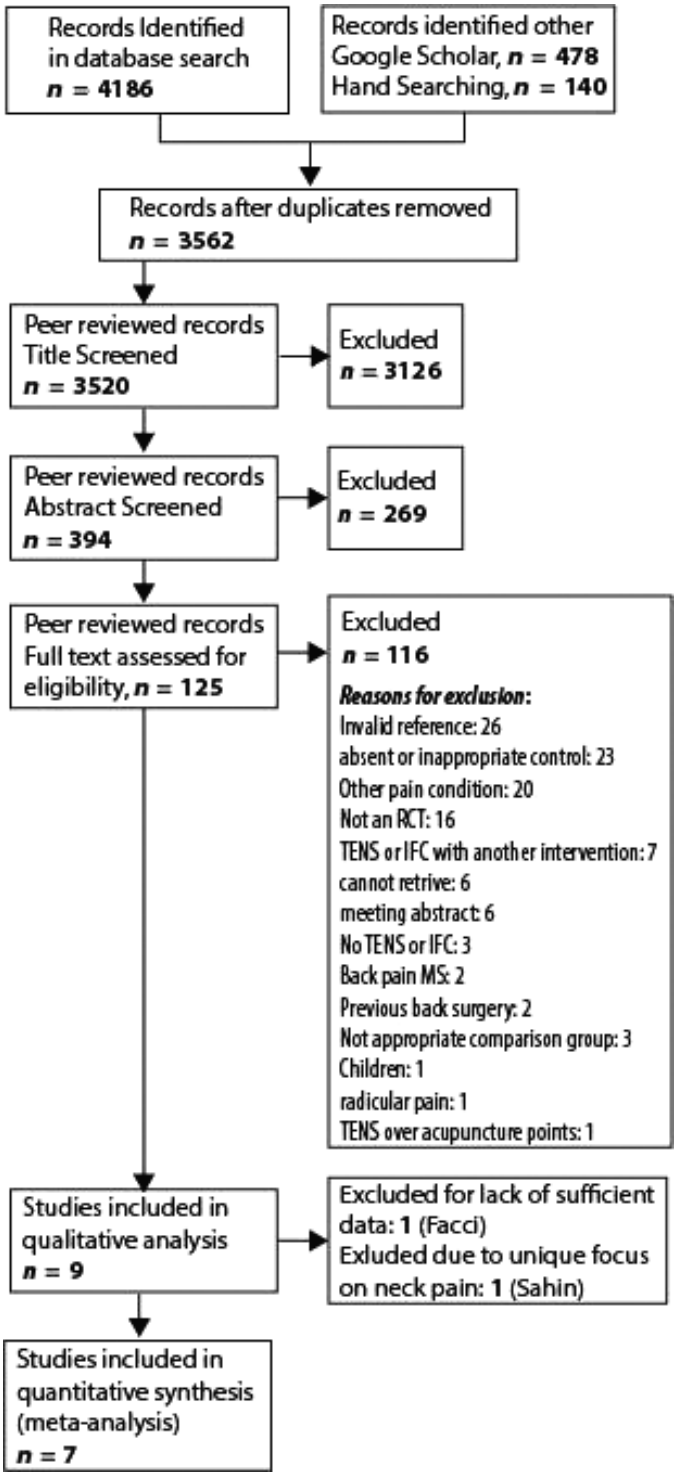

Figure 1 Flow chart of the search and selection results.

high frequency in the following 2 weeks (Deyo et al., 1990). Only four studies reported the waveform (Marchand et al., 1993; Topuz et al., 2004; Itoh et al., 2009; Facci et al., 2011).

In general, studies reported electrode sites over lumbosacral region, over the area of most pain or tenderness, or on trigger points bilaterally. In most of the studies, the number of electrodes reported

Table 2 Characteristics of included studies.

Source	Population (sample size/gender/age)	Diagnosis	Intervention	Comparison group	Assessment pain tool
Alizadeh et al. (2009)	24/women/22 ± 3 years old	CLBP	TENS (n = 8)	Control (n = 8)	-
Cheing et al. (1999)	30/men and women/18–50 years old	CLBP	TENS (n = 15)	Placebo (n = 15)	VAS
Deyo et al. (1990)	145/men and women/18–70 years old	CLBP	TENS (n = 31)	Placebo (n = 29)	VAS
Facci et al. (2011)	150/not described/>18 years old	CLBP	TENS (n = 50) IFC (n = 50)	Control (n = 50)	VAS
Itoh et al. (2009)	32/men and women/61–81 years old	CLBP	IFC (n = 6)	Control (n = 7)	VAS
Kofotolis et al. (2008)	92/women/34–46 years old	CLBP	TENS (n = 23)	Placebo (n = 21)	Borg verbal rating pain scale
Marchand et al. (1993)	42/men and women/18–60 years old	CLBP	TENS (n = 14)	Placebo (n = 12)	VAS
Sahin et al. (2011)	80/men and women/18–65 years old	Chronic neck pain	TENS (n = 19)	Placebo (n = 19)	VAS
Topuz et al. (2004)	60/men and women/19–70 years old	CLBP	TENS (n = 15)	Placebo (n = 12)	VAS

Table 3 Description of stimulation parameters in included studies.

Source	Intervention	Frequency	Pulse duration	Intensity	Carrier frequency/AMF
Alizadeh and Ahmadizad (2009)	TENS	10–70 Hz	Not described	Not described	-
Cheing and Chan (1999)	TENS	80 Hz	140 μs	2–3 times of the sensory threshold	-
Deyo et al. (1990)	TENS	C: 80–100 Hz A: 2–4 Hz	Not described	C: amplitude setting of 30 A: amplitude setting of 100	-
Facci et al. (2011)	TENS	20 Hz	300 μs	According to patient's sensitivity	-
	IFC	-	-		4000 Hz/20 Hz
Itoh et al. (2009)	IFC	-	-	2–3 times of the sensory threshold	4000 Hz/122 Hz
Kofotolis et al. (2008)	TENS	4 Hz	200 μs	Strong but comfortable	-
Marchand et al. (1993)	TENS	100 Hz	125 μs	Low intensity (clear but unpainful paraesthesia)	-
Sahin et al. (2011)	TENS	C: 100 Hz A: 4 Hz Burst: 100/2 Hz	40 μs 250 μs 40 μs	C: low amplitude A: high amplitude Burst: high amplitude	-
Topuz et al. (2004)	TENS	C: 80 Hz A: 4 Hz	100 μs	C: patient's perception of paraesthesia A: maximum tolerable without muscle contraction	-

was four. Two studies did not report the number of electrodes (Marchand et al., 1993; Cheing and Hui-Chan, 1999). Information about format and method of application of electrodes was lacking in almost all studies.

3.3 Risk of bias of included studies

Fig. 2A provides a summary of risk of bias from the twelve experimental conditions tested in the nine different articles. Fig. 2B provides a justification of each rating for each study. Eight experimental conditions (five articles) were adequate for sequence generation; seven experimental conditions (four articles) had low risk for allocation concealment; eight conditions (five articles) had low risk of blinding of participants, and adequate incomplete outcome data were found in nine conditions (six articles). Blinding of outcome assessor was unclear in six experimental conditions (four articles); and funding bias was unclear in five conditions (four articles). Sample size was unclear in seven conditions (four articles) and had high risk of bias in three conditions/articles. Lastly, adequate parameters were used in eight experimental conditions (six articles), inadequate parameters were used in two conditions (one study) and unclear parameters were reported in three conditions/articles.

3.4 Comparison data

Primary outcomes evaluated in this review were pain intensity (using the visual analogue scale (VAS)) and back function (using the Oswestry Low Back Pain Disability Questionnaire or other specific function scale). As most studies assessed pain intensity with a 10 cm VAS, we converted those with a different scale to the 10 cm VAS. Kofotolis et al.

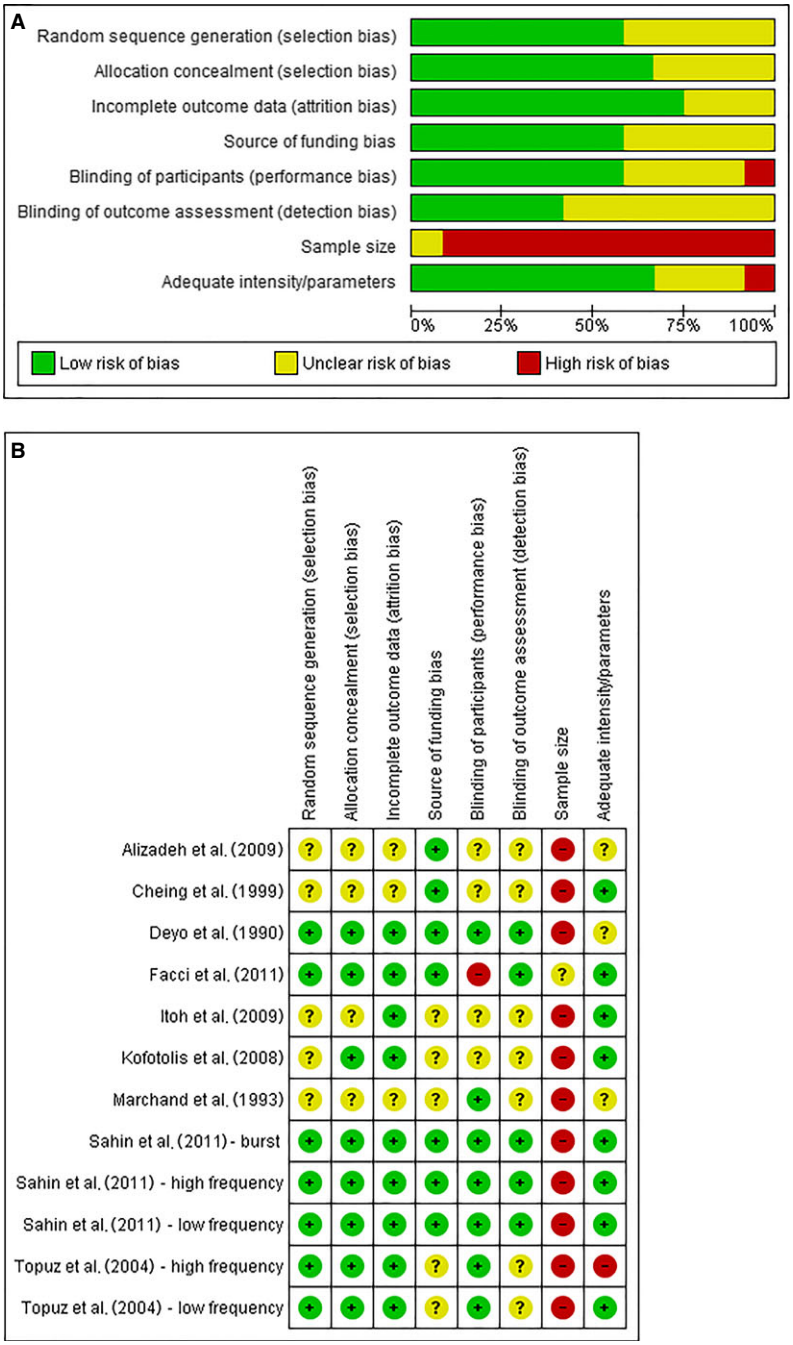

Figure 2 (A) The summary of the methodological quality for the included studies. (B) The data that support the overall methodological quality assessment in (A).

used Borg verbal rating pain scale, which we considered to be similar to VAS assessment as subjects were required to rate their pain level from 0 up to 10 (Kofotolis et al., 2008). Eight studies in this review reported pain intensity as an outcome for TENS or IFC versus placebo or control group (Deyo et al., 1990; Marchand et al., 1993; Cheing and Hui-Chan, 1999; Topuz et al., 2004; Kofotolis et al., 2008; Itoh et al., 2009; Facci et al., 2011; Sahin et al., 2011). No studies reported >50% or >30% pain reduction, an outcome suggested by the Cochrane guidelines (Higgins et al., 2011).

3.5 Pain intensity

All studies reported only resting pain, with exception of one, which assessed resting and movement pain (Topuz et al., 2004). The results of the included studies were mixed. In four studies, TENS was more effective than placebo/control intervention in reducing pain intensity (Marchand et al., 1993; Cheing and Hui-Chan, 1999; Topuz et al., 2004; Facci et al., 2011). Topuz et al. found both conventional TENS (C-TENS) and low-frequency TENS (A-TENS) (N = 12–15/group) significantly reduced current and activity pain scores immediately after intervention compared with placebo TENS group (Topuz et al., 2004). In addition, Marchand et al. and Facci et al. showed that conventional TENS (80–100 Hz) was significantly more effective than the placebo-TENS in reducing pain intensity immediately after treatment (Marchand et al., 1993; Cheing and Hui-Chan, 1999) and Marchand et al. showed an effect 1 week after the end of the treatment (N = 48) (Marchand et al., 1993). Facci et al. (N = 137) reported subjects with chronic low back pain presented greater pain reduction after 2 weeks of low-frequency TENS (20 Hz) or IFC compared with control group. Facci et al. did not use a placebo group comparison; the control group was patients who received written guidance for vertebral column care (Facci et al., 2011). Of these studies, Topuz et al. (low-frequency group), Cheing et al. (N = 30), and Facci et al. used adequate stimulation intensities (Cheing and Hui-Chan, 1999; Topuz et al., 2004; Facci et al., 2011), while the study by Marchand et al. was unclear (Marchand et al., 1993), and that by Topuz et al. was inadequate for the high-frequency group (Topuz et al., 2004).

On the other hand, four trials reported no differences in pain intensity between TENS or IFC and placebo or control group (Deyo et al., 1990; Kofotolis et al., 2008; Itoh et al., 2009; Sahin et al., 2011). Deyo et al. (N = 60–65/group) found no significant differences between TENS and placebo after 1-month treatment (Deyo et al., 1990). In this study, subjects received conventional TENS for the first 2 weeks, and then selected the mode they preferred (high frequency vs. low frequency) for the last 2 weeks; the outcome was measured 1 month after therapy. Neither Kofotolis et al. (N = 88) nor Itoh et al. (N = 15) observed statistically significant improvements in pain scores immediately or up to 3 months after low-frequency TENS or IFC intervention, respectively (Kofotolis et al., 2008; Itoh et al., 2009). Of these, Itoh et al. and Kofotolis et al. used adequate intensities of stimulation, while Deyo et al. and Alizadeh et al. used parameters that were unclear (Deyo et al., 1990; Kofotolis et al., 2008; Alizadeh and Ahmadizad, 2009; Itoh et al., 2009).

Only one study met the criteria for inclusion in individuals with neck pain (Sahin et al., 2011). In this study, Sahin and compared conventional, low frequency, and burst TENS to placebo (N = 18–19/group), and showed no significant effect before and treatment for any of the groups. Sahin used intensities that were adequate in all three active intervention groups.

3.6 Back-specific function

Five studies in this review reported back-specific function or disability outcome of TENS/IFC versus placebo-TENS/control using the Oswestry Low Back Pain Disability Questionnaire tool assessment or the Roland Morris Disability Questionnaire (RMDQ) (Topuz et al., 2004; Kofotolis et al., 2008; Alizadeh and Ahmadizad, 2009; Itoh et al., 2009; Facci et al., 2011). Alizadeh et al. (N = 8/group) and Topuz et al. reported that TENS produced greater improvements in Oswestry Disability index than the placebo or control, immediately or 3 days after the treatment (Topuz et al., 2004; Alizadeh and Ahmadizad, 2009). Facci et al., reported significant decreases in RMDQ score after TENS intervention, while Itoh et al., showed no difference in the RMDQ (Facci et al., 2011). Secondary outcomes in this review were general health, patient satisfaction and adverse effects. Topuz et al. reported improvement in general health as assessed by SF36 questionnaire for TENS groups (high and low frequency) compared with placebo TENS (Topuz et al., 2004; Sahin et al., 2011). Sahin et al. reported no significant difference between groups; however, this study analysed only the bodily pain subscale of SF36 questionnaire which may not be as sensitive as a numerical rating index (Sahin et al., 2011). Adverse effects (allergic dermatitis and skin irritation) were reported in only one trial by Deyo et al. (1990). No study reported patient satisfaction.

3.7 Meta-analysis

In all, seven studies were included for meta-analysis (Deyo et al., 1990; Marchand et al., 1993; Cheing and Hui-Chan, 1999; Topuz et al., 2004; Kofotolis et al., 2008; Alizadeh and Ahmadizad, 2009; Itoh et al., 2009). Facci et al. were excluded from meta-analysis because of the absence of data (Facci et al.,

2011). Sahin et al. were also excluded from meta-analysis because of its unique focus on neck pain (Sahin et al., 2011). Forest plots with meta-analytical statistics for TENS/IFC against placebo/control are shown separately for low back pain intensity and back function outcomes in Figs. 3 and 4, respectively.

3.7.1 Pain intensity

Meta-analysis shows TENS/IFC intervention is significantly better than placebo/control (Overall effect = −0.92; 95% CI −1.73 to −0.12; $p < 0.02$; $I^2 = 82\%$) (Fig. 3), when analysed independent of time of assessment or intensity/parameters. Note, however, the high heterogeneity between studies ($I^2 = 82\%$), and the low number of subjects ($n = 148$) included in the pooled data. When only those with adequate stimulation parameters were analysed, there was no significant effect for changes in pain intensity (Overall effect: −0.99; 95% CI −2.52 to 0.54; $p = 0.21$; $I^2 = 84\%$) (Fig. 3). Similarly, in those with inadequate or unknown stimulation parameters, there was also no effect (Overall effect: −0.95; 95% CI −2.36 to 0.47; $p = 0.19$; $I^2 = 79\%$) (Fig. 3). Again, for analysis of stimulation parameters, there was high heterogeneity and a low number of subjects. For time of pain assessment in response to the intervention, regardless of intensity parameters, TENS/IFC intervention was better than placebo/control, during therapy (Overall effect: −1.44; 95% CI −2.64 to −0.24; $p = 0.02$, $I^2 = 34\%$) (Fig. 4), but not immediately after therapy (Overall effect: −1.39; 95% CI −2.91 to 0.14; $p = 0.08$; $I^2 = 88\%$) (Fig. 4), or 1–3 months after therapy (Overall effect: −0.00; 95% CI −0.27 to 0.27; $p = 0.99$; $I^2 = 0\%$) (Fig. 4). In this analysis, while there was high heterogeneity immediately after therapy, there was moderate to low heterogeneity during therapy or 1–3 months after therapy.

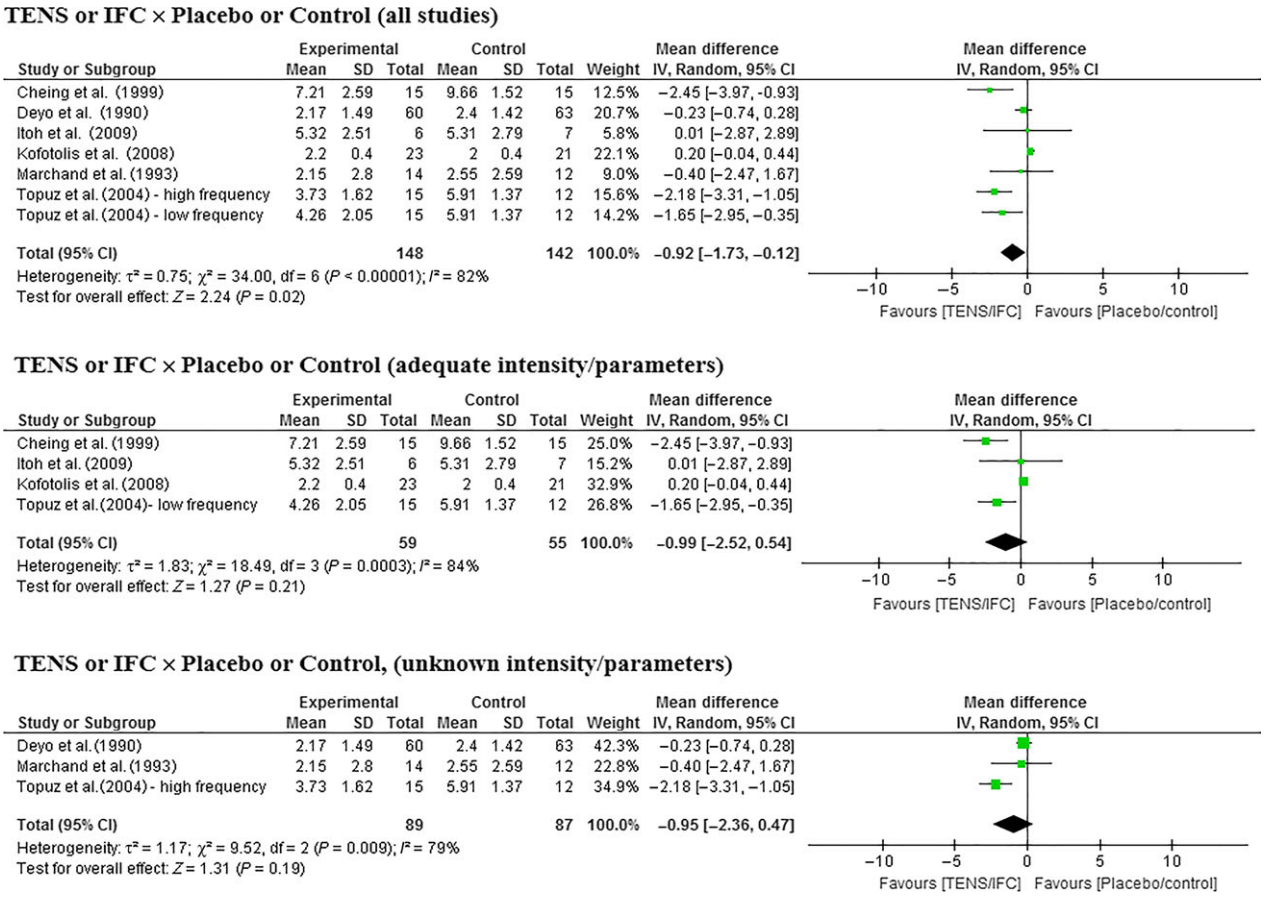

Figure 3 Forest plots showing meta-analysis results for pain intensity for all studies, and those separated by adequate and inadequate intensities. Pain intensity of the low back was assessed on a 10-point visual analogue scale or an equivalent scale.

3.7.2 Back-specific function

Meta-analysis for back-specific function, measured by self-report, shows TENS is not better than placebo (Overall effect: −0.72; 95% CI −4.13 to 2.69; $p = 0.68$; $I^2 = 71\%$) (Fig. 5) – note the high heterogeneity among studies with a low number of subjects. As for pain intensity, there were few studies and low subject numbers to include in the analysis making interpretation of subgroups unclear. For the time of assessment, TENS did not improve back function immediately after therapy (Overall effect: −0.96; 95% CI −3.83 to 1.91; $p = 0.51$; $I^2 = 49\%$) or 3 days to 3 weeks after therapy (Overall effect: 0.56; 95% CI −0.53 to 1.66; $p = 0.31$; $I^2 = 0\%$) (Fig. 5). Lastly, for studies with adequate intensity/parameters, there was no significant difference between TENS and placebo for back disability immediately after therapy (Overall effect: −0.14; 95% CI −2.04 to 2.32; $p = 0.90$; $I^2 = 25\%$) (Fig. 5).

4. Discussion

CLBP is an important public health condition due to its impact on work disability, absenteeism and treatment costs (Airaksinen et al., 2006; Dagenais et al., 2008; Koldas Dogan et al., 2008; Delitto et al., 2012) and a considerable amount of research on interventions for pain relief has been performed. TENS is a nonpharmacological modality widely used to manage pain; however, its effectiveness for patients with CLBP has been questioned (Brosseau et al., 2002; Khadilkar et al., 2008; van Middelkoop et al., 2011; Buchmuller et al., 2012). The current analysis showed that TENS/IFC intervention was superior to placebo/control for reducing pain intensity in those with non-specific low back pain during treatment, in concordance with prior systematic reviews and meta-analyses (Machado et al., 2009; Jauregui et al., 2016). However, caution should be used with interpretation of effectiveness as the

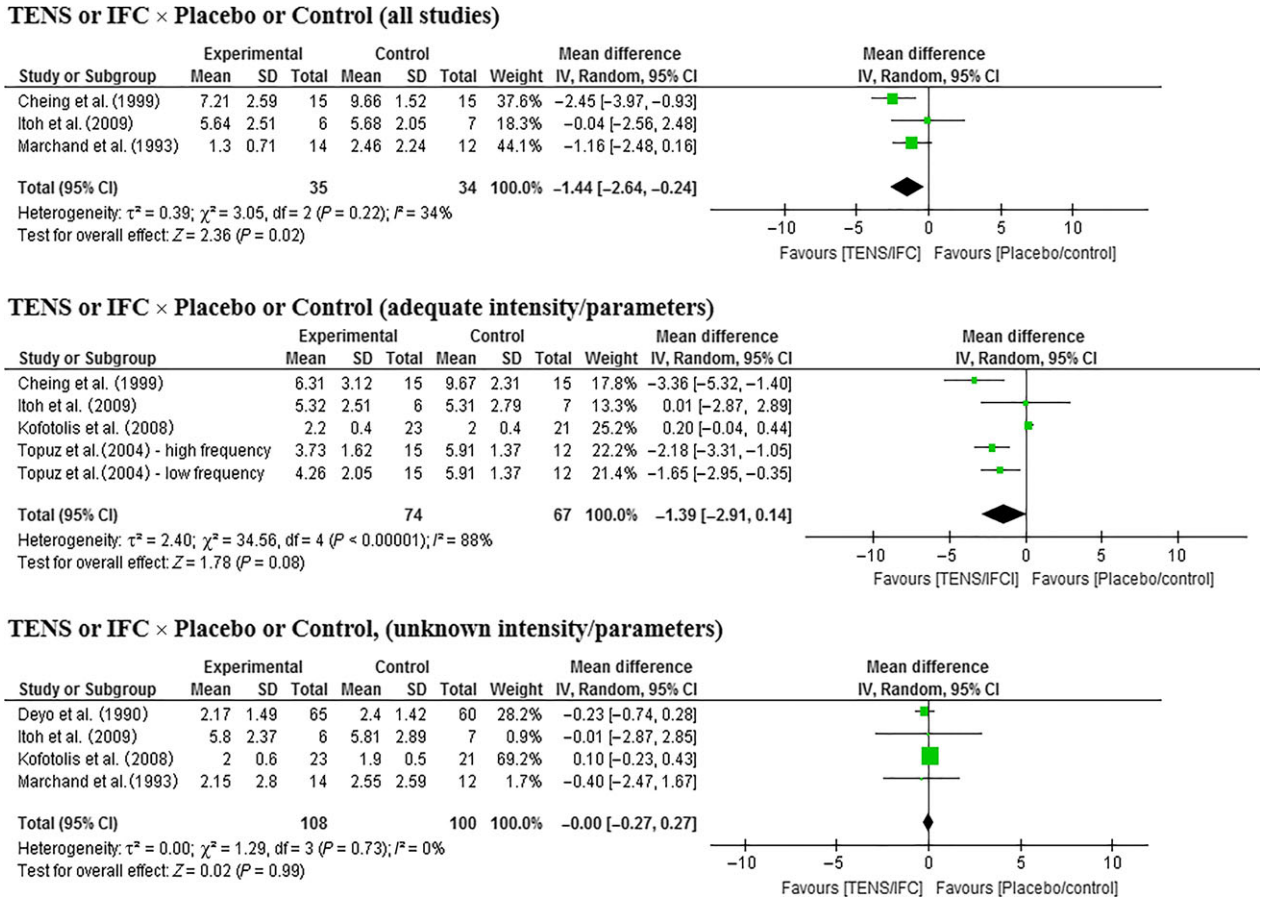

Figure 4 Forest plots showing meta-analysis results for pain intensity based on timing of outcome during therapy, immediately after therapy or 1–3 months after termination of therapy. Pain intensity (low back) outcome with VAS (0–10). Pain intensity of the low back was assessed on a 10-point visual analogue scale or an equivalent scale.

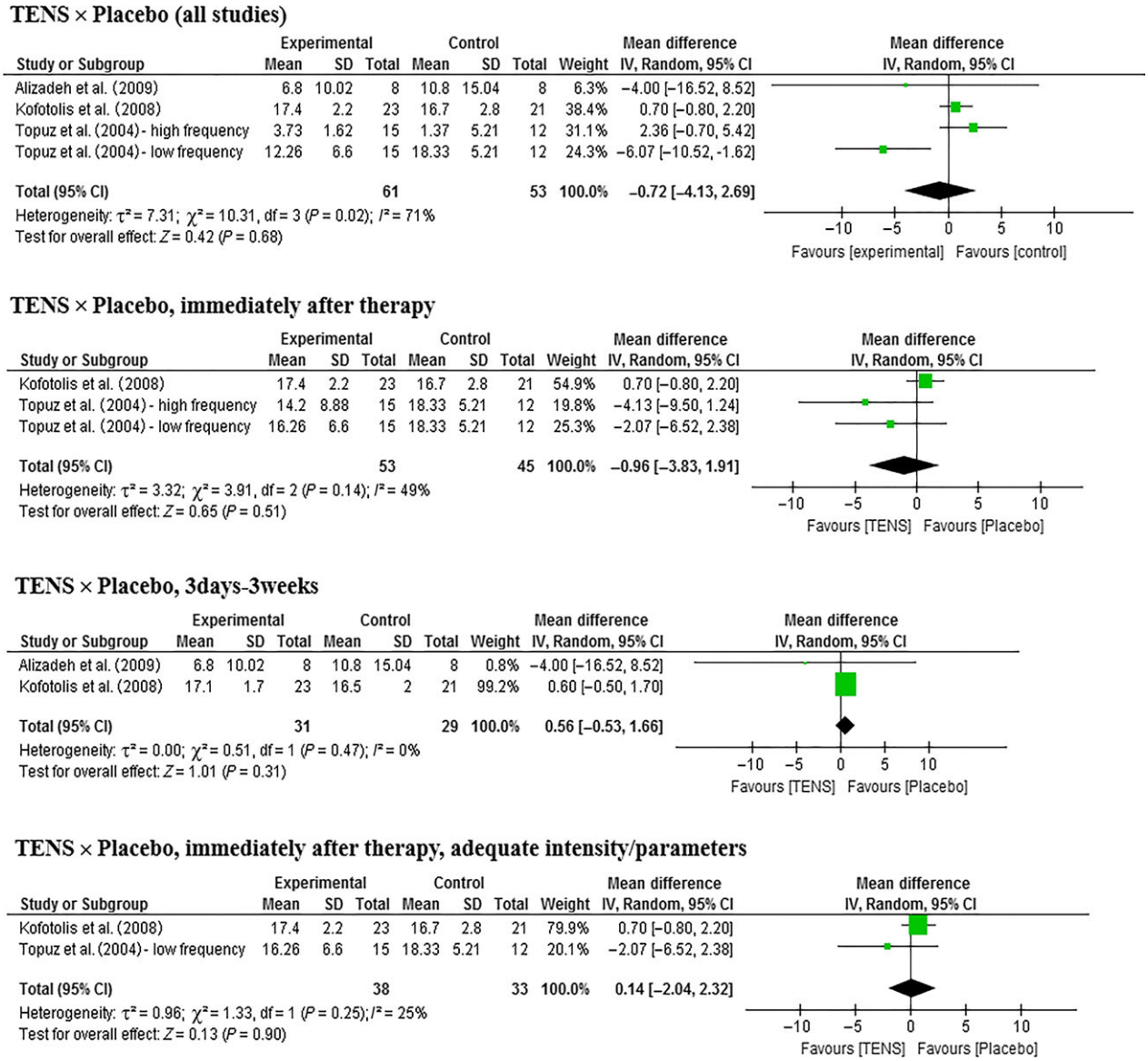

Figure 5 Forest plots showing meta-analysis results for back disability for all studies, and subanalysis based on adequate intensity and parameters, or on timing of outcome. Disability was assessed with the Oswestry disability questionnaire.

studies used in the current review and the prior review are very heterogenous (I^2 = 80%–82%) (Jauregui et al., 2016). Further, NICE guidelines and the Centers for Medicare and Medicaid Services recommend clinicians do not offer transcutaneous electrical nerve simulation (TENS) for managing low back pain (Bernstein et al., 2017; CMS.gov).

In previous studies and systematic reviews, a number of variables related to TENS application that contribute to TENS success have not been considered. Particularly, the dose of TENS (Bjordal et al., 2003, 2007; Rakel and Frantz, 2003; Rakel et al., 2010; Moran et al., 2011) and timing of the outcome measure (Melzack et al., 1983; Marchand et al., 1993; Leonard et al., 2010; Vance et al., 2012) are critical for achieving and assessing TENS effectiveness. Both of these were pointed out by Bennett and colleagues as important factors to consider in design and interpretation of the existing literature and future clinical trials (Bennett et al., 2011). To the best of our knowledge, this is the first systematic review to primarily consider the dose of TENS and timing of outcome assessment in patients with CLBP. Jauregui et al. found a statistically significant reduction in

pain intensity by TENS immediately after treatment (0.84 pre–post difference), but no effects at long-term follow-up (Jauregui et al., 2016), and Poitras and Broseeau showed there was 'clinically important and statistically significant reduction in pain intensity by TENS immediately after treatment', but no effects at long-term follow-up (Poitras and Brosseau, 2008). The high heterogeneity in the analyses that include all studies may be related to the heterogeneity in the TENS dose and outcome assessments. In the current study, for example, the heterogeneity of the studies was reduced during TENS treatment and 1–3 months after treatment, times when we expect a peak effect and no effect, respectively. Together, these data suggest that TENS effects on pain are most likely to be measured when the TENS unit is on or immediately after treatment. In contrast to effects on pain intensity, the current analysis shows no effect of TENS on disability immediately after treatment or at longer-term follow-up. This immediate effect may explain the lack of change in disability ratings, which are measures of longer-term effects.

Prior systematic reviews and meta-analysis show that intensity of TENS is important in TENS effectivenesss (Bjordal et al., 2003, 2007; Johnson et al., 2015). The current review is unique in that we performed a subanalysis based on intensity of stimulation. This analysis showed no difference in outcomes overall in studies with adequate or those with inadequate/unknown parameters of stimulation. This lack of difference in these groups, when compared to the analysis including all groups may be related to lower power due to the inclusion of only 3–4 studies with small sample sizes for each analysis. Several studies we classified as having inadequate or unknown parameters could have used appropriate intensities, which could contribute to the lack of difference between the two groups. Alternatively, intensity may not be a critical factor in effectiveness of treatment. We do not think this is the case as prior studies, specifically evaluating effects of intensity on analgesia show an increasing amount of analgesia with increasing intensities (Rakel et al., 2010; Liebano et al., 2011; Moran et al., 2011).

Interestingly, the length of time a person uses TENS, that is, duration of treatment, can effect TENS efficacy. A recent meta-analysis showed that TENS reduced pain intensity in people who were treated with TENS for less than 5 weeks but not those treated for more than 5 weeks (Jauregui et al., 2016). A possible explanation for these findings is the occurrence of analgesic tolerance due to repeated applications of TENS, as previously observed in animals (Chandran and Sluka, 2003) and human studies (Liebano et al., 2011). Thus, the number of TENS treatment sessions and time point of pain assessments seem to play an important role that should be considered in future studies.

Peak effects of TENS occur when the unit is on or immediately after stopping TENS in individuals with chronic pain (Melzack et al., 1983; Marchand et al., 1993; Leonard et al., 2010; Vance et al., 2012), and recent evidence shows that TENS is more effective for movement pain rather than resting pain (Rakel and Frantz, 2003; Dailey et al., 2013). TENS could be used effectively during physical activities, especially in patients with movement pain and kinesiophobia. Only one study assessed pain during activity and showed a positive effect for both conventional and low-frequency TENS[41]. Further studies using this interventional design should be encouraged.

Findings from several studies in patients with chronic LBP suggest central sensitization is present in a subgroup of the LBP population (Nijs et al., 2015). It is possible that this subgroup of patients with deficits in endogenous inhibition or enhanced central excitability are more likely to respond to TENS as it produces its effects by increasing endogenous opioid release and reducing central excitability (Sluka and Walsh, 2003; Sluka et al., 2013). In fact, in individuals with fibromyalgia, we show that during TENS, there is an increased in conditioned pain modulation, a measure of endogenous inhibition, and an increase in pain thresholds at sites distant to the stimulation, a measure of central excitability (Dailey et al., 2013). Thus, assessing underlying mechanisms, or matching TENS treatment to those with altered central sensitization and inhibition, could prove more effective, and future studies should pursue this as an avenue of research.

This systematic review had several limitations. We had a small number of randomized controlled trials with varying parameters for frequency, pulse duration and stimulus intensity and different outcome measures and follow-up periods. In addition, one study was excluded from meta-analysis because of the absence of data despite repeated attempts to correspond with the authors (Facci et al., 2011). Furthermore, there was only one study for neck pain (Sahin et al., 2011). The quality of the current studies is low, there was large degree of heterogeneity in the outcomes, and thus, it is difficult to make any firm conclusions regarding efficacy of TENS for chronic low back pain.

Future clinical trials will be necessary to ascertain the effectiveness of TENS on low back pain, and

these trials will need to be adequately designed to reduce bias and to ensure interpretation of results. We suggest adequate dosing of TENS and timing of outcome assessment while the TENS unit is on will be critical to ascertain TENS effectiveness. Furthermore, as our prior work shows TENS works more effectively for pain with movement (Rakel and Frantz, 2003; Dailey et al., 2013), compared to resting pain, we think it is important to differentiate these two constructs in trials on TENS. As TENS produces its greatest effects while the unit is on, outcome assessments for effectiveness should be performed while the TENS unit is on. As is often performed clinically, TENS should be provided to the subject to use at home. Adequate instructions for use should be provided that include use of at least 30 min at a time and use while they are active. Long-term use and continued effectiveness with repeated use should be examined; again outcome assessments should be performed while the TENS unit is on. However, based on existing data and systematic reviews (Jauregui et al., 2016), it is not expected that there will be long-term effects when the subject has stopped using the TENS. Importantly, as with many nonpharmacological treatment studies, most TENS trials are underpowered, and thus future studies should be designed using power calculations and will likely need at least 50 subjects per arm to be adequately powered (Bennett et al., 2011). Future systematic reviews should consider homogeneity of samples, characteristics and behaviour of pain, time of evaluation and frequency and intensity of electrical stimulus. However, unless additional clinical trials are performed using high-quality design, appropriate parameters of stimulation, and timing of assessments performed during the TENS peak effects, these data are likely to remain controversial and inconclusive for efficacy of TENS for chronic low back pain.

In conclusion, due to the low quality of the studies, and large heterogeneity among the studies, the effects of TENS on chronic low back pain are unclear. Future clinical trials are needed using a high-quality, randomized controlled trial design that consider the intensity and time of stimulation, assess multiple outcomes including pain, disability and function and include a subgroup of patients who have enhanced excitability and reduced inhibition.

Author Contributions

All authors were involved in the design of the systematic review. L.R., K.S. and R.L. wrote the initial draft of the manuscript while J.E., E.M., D.D., J.D. reviewed and edited the manuscript. J.D. performed the review of the literature, J.E. performed synthesized manuscripts. L.R., R.L., E.M. and D.D. reviewed titles, abstracts and manuscripts while KS reviewed conflicts between reviewers. L.R. and R.L. extracted data, R.L. and K.S. performed quality assessment of manuscripts.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Forest plots showing meta-analysis results for pain intensity based on stimulation parameters and timing of outcome for pain intensity.