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Systematic review

Does the pulse frequency of transcutaneous electrical nerve stimulation (TENS) influence hypoalgesia? A systematic review of studies using experimental pain and healthy human participants

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Abstract

Objectives To determine the hypoalgesic effect of pulse frequency of transcutaneous electrical nerve stimulation (TENS) when all other TENS parameters are held constant.

Data sources Systematic review of studies using experimentally induced pain on healthy participants where there was a head-to-head comparison of different pulse frequencies. AMED, CINAHL, EMBASE, Inspec, PEDro, Pre-CINAHL, PsycARTICLES, PubMed, SPORTDiscus were searched in September 2006.

Review methods Inclusion criteria were studies that directly compared two or more pulse frequencies head-to-head and recorded outcome as change in pain threshold or pain intensity. Studies were excluded if pulse intensity, pulse pattern, or pulse duration of TENS were not standardized between groups. Two reviewers judged the trial outcome independently. Primary outcome was a report of a statistically significant difference between pulse frequencies for pain threshold or intensity at any time point through the experiment.

Results Twenty studies were identified, of which 13 experimental studies from 12 published reports were included for review. Ten studies found no statistically significant differences in hypoalgesia between pulse frequencies. Of the three studies judged as positive outcome, one reported that 100 pulses per second (pps) was superior to 10 pps; one that 4 pps was superior to 100 pps; and one that 5 pps and 80 pps were superior to 2 pps.

Conclusion Evidence from experimental pain studies suggests that TENS pulse frequency does not influence hypolagesia when its pulse intensity, pulse pattern, and pulse duration are kept constant. Inadequate sample sizes may have generated false negative findings in some studies.

Keywords: Transcutaneous electrical nerve stimulation (TENS); Analgesia; Experimental pain; Healthy subjects; Systematic review

Introduction

Transcutaneous electrical nerve stimulation (TENS) is commonly used for the treatment of pain [1–4]. It has long been believed that the electrical characteristics of TENS influence the magnitude of pain relief and as a consequence TENS manufacturers have manipulated the technical specifications of devices in an attempt to improve efficacy [1]. Nowadays TENS devices allow the user to alter pulse amplitude (mA), pulse duration (μs), pulse pattern (continuous, burst, modulation) and pulse frequency (pulses per second, pps) in order to selectively recruit different populations of nerve fibres. Opinion leaders claim that pulse frequency is a key determinant of TENS outcome [1,3–7]. However, long term users of TENS often select pulse frequency *ad hoc* and for reasons of comfort [8,9]. The findings of studies using healthy humans exposed to experimental pain, which manipulated TENS parameters under laboratory controlled conditions, are often used to support claims that pulse frequency may be a key determinant of hypoalgesic effect [1,4]. To date there has been

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no attempt to assess the published literature in a systematic fashion by comparing pulse frequencies head-to-head when all other parameters are held constant.

TENS interventions tend to be described according to the technical characteristics of TENS as 'high frequency, low intensity' (conventional TENS) or 'low frequency, high intensity' (acupuncture-like TENS). This has resulted in unclear reporting of TENS interventions because it fails to specify the physiological intention of TENS. In this regard, the physiological intention of conventional TENS is to selectively activate non-noxious skin afferents (Aβ fibres) without simultaneously activating noxious skin afferents (Aδ- and C-fibres) as this leads to segmental anti-nociception [4,10]. Theoretically, high frequency (~10–250 pps), low intensity (non-painful) currents would be most efficient in selectively activating Aβ fibres [3,11]. In practice, Aβ afferent activity is achieved by the user reporting 'strong but comfortable' non-painful electrical paraesthesia beneath the electrodes. The physiological intention of acupuncture-like TENS is to activate small diameter non-noxious muscle afferents through the generation of a muscle twitch as this elicits extrasegmental anti-nociceptive mechanisms via descending pain inhibitory pathways [6,12]. This is achieved by delivering TENS at low frequencies at high but non-painful intensities over muscles. Pulsed electrical currents given at low frequency were found to be uncomfortable in producing muscle twitches so low frequency trains of pulsed currents, termed 'burst mode TENS', were used instead [3,6,12–14].

It is often written in textbooks [1,5,15,16], chapters [3,4,6,7] and user guides accompanying TENS devices [17–19] that certain pulse frequencies are superior to others for treating particular conditions. Laboratory studies on healthy humans exposed to an external stimulus to create the experience of pain (i.e. experimental pain) are often used to support these claims. Experimental pain studies are used to assess analgesic efficacy because they are relatively safe and they enable investigators to control pain experience and adherence to the treatment intervention. There is no doubt that experimental pain does not reflect biopsychosocial factors that influence pain experience in the clinical setting but it does contribute to knowledge about treatment response for transient pain, which aids understanding of the early processing of clinical pain. Hence, studies on healthy human subjects are often used as a precursor to clinical trials [20,21].

Closer examination of this supporting evidence reveals that inferences about the relative effects of pulse frequency are based on active group comparisons with sham/control group or when more than one TENS parameter has been manipulated simultaneously. However, investigations which compare the hypoalgesic effects of pulse frequencies head-to-head are necessary to determine the differential effects of pulse frequency of TENS. The purpose of this systematic review of studies using experimentally induced pain in healthy human subjects was to determine the hypoalgesic effects of TENS pulse frequency when other TENS parameters are kept constant.

Methods

Search strategy

A literature search for eligible studies was undertaken in September 2006 using electronic databases AMED (1985–2006), CINAHL (1982–2006), EMBASE (1980–2006), Inspec (1969–2006), PEDro (1929–2006), pre-CINAHL (1982–2006), PsycARTICLES (1985–2006), PubMed (1951–2006) and SPORTDiscus (1985–2006). MeSH and/or free text words were: 'transcutaneous electric nerve stimulation [MeSH]', 'transcutaneous electrical nerve stimulation', 'electric stimulation therapy [MeSH]', 'TENS', 'electrotherapy', 'pain [MeSH]' and 'pain measurement [MeSH]'. Articles were screened for relevance against the inclusion criteria by the primary investigator (CC). Initially study titles and abstracts were used to identify potential studies and full published reports obtained. The reference lists of retrieved or relevant articles were also screened for reports not identified through electronic searches.

Inclusion criteria

To be included in this review studies must have:

- Been published as a full experimental report.
- Used experimental pain on healthy human participants.
- Directly compared at least two or more pulse frequencies head-to-head using a continuous pattern of pulse delivery. For experimental reports which did not explicitly state which pulse pattern was used reviewers included studies if they were confident that TENS was not delivered using other pulse patterns (i.e. did not use burst or modulated pulse patterns).
- Recorded pain outcome as change in pain threshold or pain intensity. These are commonly used outcomes to quantify hypoalgesia in such studies. Hypoalgesia is defined as diminished pain in response to a normally painful stimulus including raised threshold [22].
- Delivered TENS using a 'standard TENS device' which we have defined as biphasic pulsed currents delivered in a repetitive manner with pulse durations between 10 μs and 1000 μs and pulse frequencies between 1 pps and 250 pps [14].
- Intensities that were above sensory perception threshold and described using terms such as 'strong' and/or 'comfortable' and/or 'tolerable' [23].

Studies and/or comparisons were excluded if:

- The effect of pulse frequency could not be isolated because other TENS settings were not standardised.
- TENS intensities were described as 'barely perceptible'.
- Hypoalgesia using a verbal report of pain was not an outcome measure (e.g. nerve conduction or withdrawal reflex).
- Pulse patterns other than 'continuous' ('normal') were used.

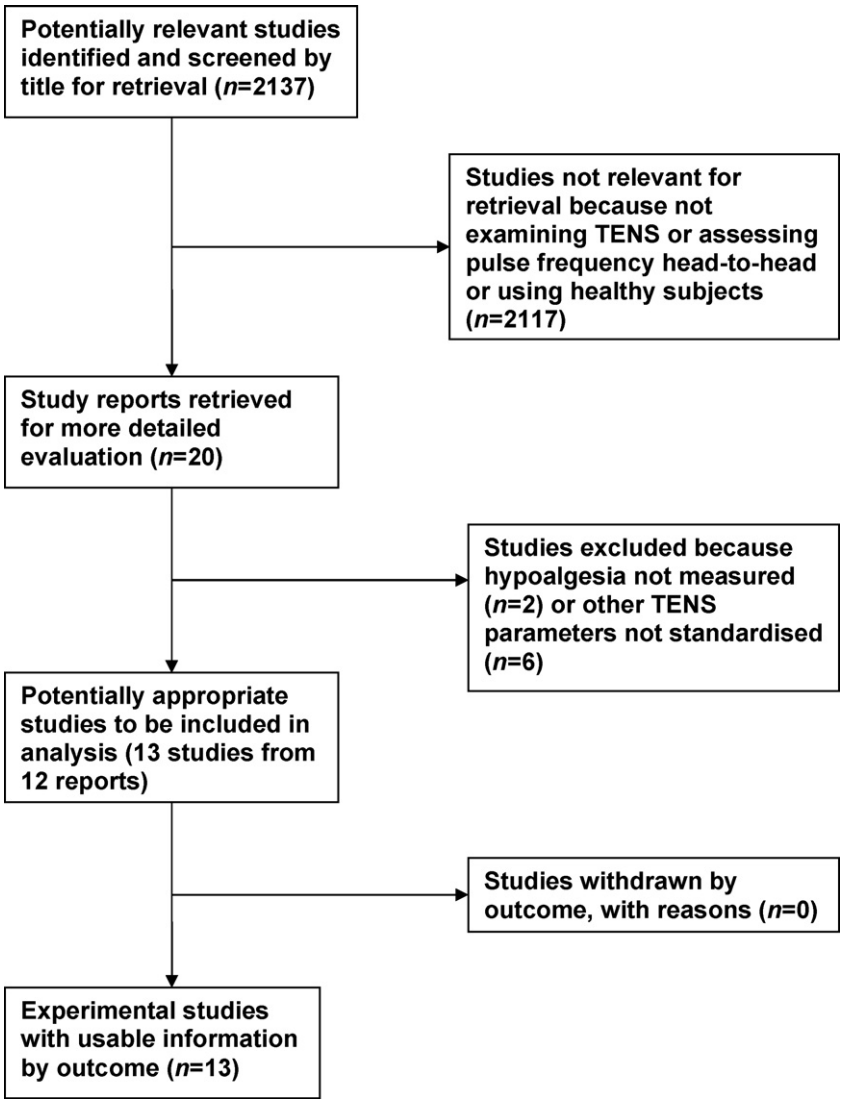

Fig. 1. QUOROM statement flow chart [64].

Data extraction and analysis

Two reviewers (CC and MJ) extracted information and judged trial outcome independently. Outcome was dichotomised as either positive, where one frequency was statistically different to another, or negative, where one frequency was not statistically different to another. A statistically significant reduction in pain at any time point through the experiment was taken as a difference between the groups. Disagreements in judgements were logged and a final decision was made following a discussion between the reviewers in the presence of a third investigator (GT), who had not taken part in the original data extraction and trial judgement process.

Results

Over 2100 articles were identified in the initial search of the electronic databases, although the majority were found to be not relevant during screening of study title and abstract. Twenty full published reports were potentially relevant and retrieved (Fig. 1). Two of these studies were excluded because hypoalgesia was not an outcome measure [24,25]. Six studies were excluded because pulse intensity, pulse duration or stimulation site were not standardised between groups, making direct head-to-head comparisons and subsequent isolation of pulse frequency effects impossible [26–31].

Twelve studies met the inclusion criteria for review (Table 1). The report by Walsh *et al.* [32] examined pulse frequency on mechanical pain threshold, which was included in the analysis, and also peripheral nerve conduction, which was excluded from the analysis. The reports by Walsh *et al.* [33] and Cramp *et al.* [34] examined the effect of pulse frequency on electrical pain using visual analogue scales, which was included in our analysis, and the RIII and H-reflex, which was excluded in our analysis. The report by Foster *et al.* [35] contained two separate experimental studies and both were included in our analysis. The intervention group receiving

Table 1
Studies included in this review

Reference	Pain models and sample size	TENS pulse frequency (pps)	TENS pulse duration (μs)	TENS subjective intensity	TENS paraesthesia	Comparison group	Outcome measurement(s)	Authors' conclusion	Reviewers' judgment
Heat pain									
de Tommaso *et al.* [37]	CO_2 laser	10	200	SBC	Within site of pain	2 TENS groups	SPR, peak-to-peak amplitude of LEPs	100 pps > 10 pps in SPR	100 pps > 10 pps
	16 ($n = 8$ per group)	100							
Chakour *et al.* [36] [a]	CO_2 laser	2	200	SBC	Within site of pain	8 TENS groups	Pain threshold	No difference	No difference
	80 ($n = 10$ per group)	5							
		80							
		2	200	Tolerant				5 pps, 80 pps > 2 pps	5 pps, 80 pps > 2 pps
		5							
		80							
Cold pain									
Foster *et al.* [35]	Cold-pressor	4	200	SBC	Proximal to site of pain	2 TENS groups, placebo, control	Pain threshold	No difference	No difference
	32 ($n = 8$ per group)	110							
Johnson *et al.* [40]	Cold-pressor	10	200	SBC	Proximal to site of pain	5 TENS groups, sham, control	Pain threshold, pain tolerance, EPQ	No difference	No difference
	83 ($n = 7$ to 12 per group)	20							
		40							
		80							
		160							
Ashton *et al.* [39] [b]	Cold-pressor	8	200	SBC	Proximal to site of pain	2 TENS groups, acupuncture group, placebo	Pain threshold, pain tolerance, EPQ	No statistical difference although 8 pps but not 100 pps elevated pain threshold	No difference
	46 ($n = 10$ to 13 per group)	100							
Electrical pain									
Walsh *et al.* [33]	Electrical stimulation (withdrawal reflex)	4	50	SBC	Proximal to site of pain	4 TENS groups, control	VAS, RIII reflex, H-reflex	No difference	No difference
	50 ($n = 10$ per group)	110							
		4	200	SBC					
		110							
Cramp *et al.* [34]	Electrical stimulation (withdrawal reflex)	5	125	SBC	Proximal to site of pain	3 TENS groups, 3 IFT groups, control	VAS, RIII reflex, H-reflex	No difference	No difference
	70 ($n = 10$ per group)	100							
		200							
Barr *et al.* [42]	Electrical stimulation	30	N/A	DAC	Proximal to site of pain	Repeated 7 different TENS interventions per group	Pain threshold, pain tolerance	No difference in pain threshold	No difference
	28 ($n = 28$ per group)	60							
		85							
Mechanical pain									
Walsh *et al.* [43]	Pressure algometer	4	50	SBC	Proximal to site of pain	4 TENS groups, control	MPT, TT, CAP	No difference in MPT	No difference
	50 ($n = 10$ per group)	110							
		4	200	SBC					
		110							

Table 1 (*Continued*)

Reference	Pain models and sample size	TENS pulse frequency (pps)	TENS pulse duration (μs)	TENS subjective intensity	TENS paraesthesia	Comparison group	Outcome measurement(s)	Authors' conclusion	Reviewers' judgment
Walsh *et al.* [32]	Pressure algometer	4	50	SBC	Proximal to site of pain	4 TENS groups, placebo, control	MPT	TENS groups > control	No difference
	48 ($n = 8$ per group)	110							
		4	200	SBC					
		110							
Ischaemic pain									
Foster *et al.* [35]	Sphygmomanometer cuff	4	50	SBC	Proximal to site of pain	4 TENS groups, placebo, control	VAS, MPQ	No difference	No difference
	48 ($n = 8$ per group)	110							
		4	200	SBC					
		110							
Walsh *et al.* [38]	Sphygmomanometer cuff	4	287	SBC	Proximal to site of pain	2 TENS groups, placebo, control	VAS, MPQ	4 pps > 110 pps on VAS	4 pps > 110 pps
	32 ($n = 8$ per group)	110							
Delayed onset muscle soreness (DOMS)									
Craig *et al.* [44]	Eccentric exercise	4	200	SBC	Within site of pain	2 TENS groups, placebo, control	VAS, MPT, MPQ, elbow ROM	No difference in VAS, MPT and MPQ	No difference
	48 ($n = 12$ per group)	110							

Note: Many studies included control and treatment groups which were excluded from our head-to-head analysis of TENS pulse frequency. Hence, stated study sample size will be larger than the aggregate of groups extracted for analysis (represented by *n* per group).

Abbreviations: CAP, compound action potentials; DAC, distinct and comfortable; DOMS, delayed onset muscle soreness; EPQ, Eysenck personality questionnaire; IFT, interferential therapy; LEPs, CO2 laser evoked potentials; MPQ, McGill pain questionnaire; MPT, mechanical pain threshold; N/A, not available; ROM, range of motion; SBC, strong but comfortable; SPR, subjective perception (pain) rating; TENS, transcutaneous electrical nerve stimulation; TT, tactile threshold; VAS, visual analogue scale.

[a] 2000 Hz was excluded because it was delivered using sinusoidal currents rather than biphasic pulsed currents as used in the other groups.

[b] The authors did not make a direct statistical comparison of 8 pps with 100 pps.

2000 Hz as sinusoidal currents in the study by Chakour *et al.* [36] was excluded from our analysis because it did not meet our eligibility criteria. Thus, there were 12 reports of 13 experimental studies with usable information by outcome.

Several approaches were used to induce experimental pain, including heat ($n = 2$), electrical ($n = 3$, not including Walsh *et al.* [32]), cold ($n = 3$), mechanical ($n = 2$), ischaemia ($n = 2$) and delayed onset muscle soreness ($n = 1$) methods. A total of 631 participants recruited in the included studies. Study reports often stated that subjects were randomised into intervention groups although it is more likely that block randomisation had been used because groups often contained equal numbers of subjects. Similarly, study reports often claimed that a double blind approach was used although details about the assessor, participant and person administering TENS were limited. Furthermore, true blinding would be impossible as participants would experience differences in the sensations generated by different frequencies of TENS.

Studies demonstrating effects for pulse frequency

Only three studies reported a significant difference in the magnitude of hypoalgesia between pulse frequencies. de Tommaso *et al.* [37] reported that 100 pps was superior to 10 pps in reducing painful heat administered to 16 participants ($n = 8$ per group) using a CO_2 laser stimulus (10.6 μm wavelength, 2.5 mm beam diameter, 45 ms). TENS was delivered on the ventral surface of the right forearm using electrodes applied to either side of the stimulus at a 'strong but comfortable' intensity and a pulse duration of 200 μs. Subjective perception/pain rating and peak-to-peak amplitude of laser evoked potentials were taken before, immediately after and almost 50 minutes after 15 minutes of TENS. A pulse frequency of 100 pps produced a significantly larger decrease in pain rating when compared to 10 pps, although it was not possible to ascertain the magnitude of this difference from the study report.

Chakour *et al.* [36] using 10 participants per group reported that 5 pps and 80 pps given as biphasic square waves were superior to 2 pps in reducing painful heat administered using a CO_2 laser stimulus (10.6 μm wavelength, 1–100 W power, 5 mm beam diameter, 50 ms). This effect was observed when TENS was high enough to produce distinct noxious pricking (maximal intensity), but was not observed when TENS was given at a 'strong but comfortable non-painful paraesthesia' (sub-maximal intensity). Pain threshold was taken during a 5-minute TENS intervention period and the results indicated that similar changes were observed for all frequencies except for 2 pps, which was less effective than other frequencies when given at the maximal intensity (i.e. a mean change of 1 W from baseline compared to a change of between 8 W and 12 W in the other groups). We judged this study as being positive outcome based on the finding that 5 pps and 80 pps reduced the threshold to experimental thermal pain when compared to 2 pps when TENS was given at a 'maximal' intensity. It is very possible that this finding was due to an erroneous result for the 2 pps group, and the authors themselves concluded that there were no frequency effects.

The study by Chakour *et al.* [36] would have been judged as negative outcome if we had used the results obtained when TENS was given at a 'strong but comfortable' intensity because there were no differences between pulse frequencies. This differs from de Tommaso *et al.* [37], who found significantly larger reductions in pain for 100 pps compared to 10 pps. This discrepancy may be due in part to the use of different outcome measures in the studies, with de Tommaso *et al.* [37] using a 10-point verbal category scale to measure pain intensity and Chakour *et al.* [36] measuring pain threshold in watts. In their study report Chakour *et al.* [36] concluded that frequency effects were negligible between the groups.

Walsh *et al.* [38] reported that 4 pps was superior to 100 pps for reducing ischaemic pain induced by the submaximal effort tourniquet test in 32 female healthy participants who were randomly assigned into one of four groups ($n = 8$ per group): 110 pps TENS, 4 pps TENS, placebo TENS and no treatment control. TENS was delivered at a 'strong but comfortable' intensity via two electrodes placed over the ipsilateral Erb's point and lateral to C6 and C7 vertebral spines. Ischaemic pain was induced over a 12 minute period and pain intensity measured using visual analogue scales and the McGill Pain Questionnaire respectively. There were significant differences in visual analogue scale but not McGill Pain Questionnaire scores between groups, with the 4 pps TENS group showing a larger hypoalgesic effect than the 100 pps group.

Studies demonstrating no effects for pulse frequency

Ten of the 13 experimental studies reported no differences in hypoalgesia between pulse frequencies when all other TENS characteristics were held constant. The findings of Walsh *et al.* [38] that 4 pps was superior to 100 pps, when pulse duration is 287 μs, for reducing ischaemic pain were not replicated by a follow-up study by the same investigators. Foster *et al.* [35] reported no differences in visual analogue scales and McGill Pain Questionnaires between 110 pps and 4 pps when pulse durations were 50 and 200 μs. It is noteworthy that Walsh *et al.* [38] used a pulse duration of 287 μs and Foster *et al.* [35] used 50 μs and 200 μs, although such differences seem small (especially between 287 μs and 200 μs) and unlikely to have contributed to the discrepancies in study outcome.

Ashton *et al.* [39], Johnson *et al.* [40] and Foster *et al.* [35] used the cold-pressor pain technique to assess the effects of TENS in healthy young participants. Cold-pressor stimulation has been successfully used as a model of experimental pain to investigate analgesic interventions [41]. Ashton *et al.* [39] found no significant differences between 100 pps and 8 pps on pain threshold or pain tolerance in the hand ($n = 10$–13 per group) when TENS was administered at a 'strong but comfortable' intensity (200 μs pulse duration) via electrodes (8 cm^2 each) on the ventral surface of the forearm

for 20 minutes. Johnson *et al.* [40] working with the same group found no difference in pain threshold or pain tolerance between 10 pps, 20 pps, 40 pps, 80 pps and 160 pps ($n = 12$ per group) when TENS was delivered at a 'strong but comfortable intensity' (200 μs pulse duration) to the ventral surface of the forearm. Most pulse frequencies produced a significant elevation of pain threshold when compared to sham TENS. Foster *et al.* [35] reported no significant differences in cold-induced pain threshold in the hand between 110 pps and 4 pps ($n = 8$ per group) when TENS was given at a 'strong but comfortable' intensity (200 μs biphasic pulse) applied to the ventral surface of the forearm.

Studies using noxious electrical stimulation on healthy humans failed to demonstrate effects between pulse frequencies. Barr *et al.* [42] assessed 30 pps, 60 pps or 85 pps given as either a monophasic or biphasic wave at a 'distinct and comfortable' intensity ($n = 28$ per group). Noxious electrical stimulation was induced on the distal phalanx and palm on the dominant hand just before and after a treatment and each TENS intervention was delivered on the ventral surface of the forearm for 4 minutes. No significant differences were found between different pulse frequencies on pain threshold or pain tolerance, although pain tolerance increased significantly for 60 pps and decreased significantly for 30 pps and 85 pps when compared to pre-treatment, but there was no direct comparison made between the TENS pulse frequency groups. Using noxious electrical stimulation lateral to the malleolus over the course of the sural nerve, Cramp *et al.* [34] ($n = 10$ per group) found no significant difference in the rating of pain intensity to an electrical stimulus used to elicit an RIII reflex before, during and 30 minutes following TENS and interferential therapy given at 5 pps, 100 pps and 200 pps. Walsh *et al.* [33] ($n = 10$ per group) using similar methodology also found no significant difference between TENS given at a 'strong but comfortable' intensity and 110 pps or 4 pps and either 200 μs or 50 μs.

Both Walsh *et al.* [32] ($n = 8$ per group) and Walsh *et al.* [43] ($n = 10$ per group) reported no difference in the mechanical pain between 4 pps and 110 pps given at a 'strong but comfortable' intensity using 50 μs or 200 μs pulses. All active TENS groups produced significant effects compared to control and placebo groups. Craig *et al.* [44] ($n = 12$ per group) reported no frequency effect for pain intensity rating, mechanical pain threshold or dimensions measured using the McGill Pain Questionnaire for induced delayed onset muscle soreness on the elbow flexors. TENS was applied at a 'strong but comfortable' intensity (200 μs pulse duration) for 20 minutes on the musculo-tendinous junction of the biceps brachii at 110 pps and 4 pps.

Discussion

It is often written that TENS outcome is a function of the site of stimulation and the electrical characteristics of TENS, including pulse amplitude, duration and frequency. These claims are based on primary research that fails to isolate the effect of individual variables. Often primary research undertakes comparisons between 'high intensity, low frequency' TENS with 'low intensity, high frequency' TENS and observed outcomes could be due to any combination of high or low intensity with high or low frequency. Nevertheless, study investigators often infer that pulse frequency is a key determinant of outcome. The purpose of our review was to evaluate, for the first time, primary research that isolated the effect of pulse frequency while other parameters were kept constant. We felt it important to try to ascertain the direct influence of pulse frequency when TENS is administered in its conventional form, i.e. generating a non-noxious electrical paraesthesia within or immediately proximal to the site of pain. We only included studies that explicitly standardised the intensity of stimulation at a level rated by participants as 'strong but comfortable' or 'non-noxious electrical paraesthesia' (i.e. the way that TENS is conventionally given in clinical practice). The alternative approach of standardising output according to pulse amplitude (i.e. mA) is fraught with difficulties because of inter-participant variability in sensory detection thresholds to TENS. Furthermore, many studies do not report TENS amplitude, and when they do, they rarely report it in relation to milliamps above sensory detection threshold.

Despite much published literature on TENS, only 20 experimental studies on different pulse frequencies of TENS using healthy participants were found. Of these, 13 experimental studies examined the effects of different pulse frequencies when all other TENS parameters were kept constant. Our approach resulted in the exclusion of some TENS studies that were methodologically robust [30,31]. Ten studies reported no differences in the hypoalgesic effects of different pulse frequencies of TENS although studies included multiple group comparisons, multiple outcome measures and small subject sample sizes. The three studies that we judged to demonstrate pulse frequency effects were not convincing. Chakour *et al.* [36] reported that 5 pps and 80 pps were superior to 2 pps but only when given at a 'maximal intensity' and not when given at a 'strong but comfortable level', which is the way it is used in clinical practice. de Tommaso *et al.* [37] reported that 100 pps was better than 10 pps and Walsh *et al.* [38] reported that 4 pps was better than 110 pps when TENS was delivered at a 'strong but comfortable' intensity. Table 1 highlights that some trials used differing pulse durations but these were only included if comparisons between two pulse frequencies could be made for a particular pulse duration. Our analysis demonstrates that pulse duration had no bearing on outcome. There were no differences in the outcome of studies using 50 μs, 125 μs and 200 μs. Seven out of the nine studies using 200 μs found no difference between pulse frequencies. The three studies reporting differences between pulse frequencies used pulse durations of 287 μs and 200 μs ($n = 2$).

Three conclusions are possible from our review: (i) pulse frequencies are equally effective; (ii) pulse frequencies are

equally ineffective; (iii) the studies were inadequate to detect a difference between pulse frequencies.

An insight into whether pulse frequencies were or were not effective can be obtained by examining studies that compared active TENS with a no-treatment control and/or a sham TENS control. Four out of 10 studies reported that active TENS was better than a no treatment control [38,43,32,40] and two out of seven studies reported that active TENS was better than a sham (dummy) TENS [38,40]. However, this analysis cannot establish with any degree of certainty that active TENS was not superior to sham TENS because our review has only included studies that compared pulse frequencies head-to-head. A significant number of additional studies that have compared TENS against sham TENS may be available in the literature and therefore a separate review of studies comparing TENS against a sham control is needed.

The failure to detect differences between active and sham TENS, and between TENS pulse frequencies may be due to limitations in study methodologies which reduce the sensitivity (internal validity) of the analgesic assay. Most experimental studies included in this review used inadequate sample sizes and this would increase the likelihood of reporting a type II error (false negative). Experimentally meaningful effect sizes were rarely stated in experimental reports and only a few studies performed a power calculation to establish appropriate sizes. Only one study used more than 20 participants per group [41], most others used fewer than 10 participants per group. A retrospective calculation of the sample size required to achieve 80% power (alpha set at 0.05) for one of our own studies [40] which was included in this review highlights the problem. Our original study used 12 participants per group, although 37 participants per group would be necessary to detect a 10-second difference in cold-pressor pain threshold (standard deviation set at $\pm$15 seconds) and 143 participants necessary to detect a 5-second difference [45]. Whether a change of 5 seconds or 10 seconds is considered experimentally meaningful is open to debate, but the smaller the difference between pulse frequencies the less likely they are to translate into effects that are physiologically and ultimately clinically meaningful. Carroll *et al.* [46] estimated that randomised controlled clinical trials of TENS would need at least 40 patients in each arm of the trial in order to detect clinically meaningful effects.

Shortcomings in the psychophysical methods used to quantify pain threshold or intensity to an experimental pain stimulus may affect study outcome [21,47]. All techniques rely on a judgment about the presence and/or magnitude of the experimental stimulus. Tools used to measure subjective rating of pain intensity, such as the visual analogue scale, and pain threshold have known validity and reliability [48–50], but judgements are compromised because they are made against a pain stimulus that has changing temporospatial dimensions. Good test-retest reliability has been reported for pain thresholds and pain intensities measured using pressure algometers [51], the cold pressor technique [39], electrical stimuli [52] and a CO_2 laser [53], although all techniques have limitations [21,54,55]. For example, faster rates of application of force can lead to overestimates of pain threshold measured using pressure algometers [56]. Similarly, cold pain intensity rises rapidly within the first minute of the cold pressor test, which can overestimate pain threshold. In the cold pressor pain test pain intensity measurements are compromised by numbness developing in the submerged limb. Repeated application of painful stimuli can also lead to sensitisation and a lowering of thresholds [57]. In addition to these difficulties studies on TENS require participants to make judgements whilst experiencing TENS-induced paraesthesia close to or within the site of experimentally induced pain. The interaction between sensations of TENS paraesthesia and pain has received little attention in the literature, although Woolf *et al.* [58] reported that TENS effects differ according to the sensory modality of the experimental pain intervention. When these difficulties are taken into account it is likely that the majority of experimental studies included in our review lacked the internal sensitivity necessary to be an effective analgesic assay.

It is also known that many studies on TENS fail to use an adequate TENS technique [23]. TENS effects are maximal when administered at the site of pain to generate a strong but comfortable electrical paraesthesia [3,59,60]. Because of technical difficulties in accessing the site of pain, only three of the 13 included experimental studies generated TENS paraesthesia within the site of pain [36,44,60]. It is not possible to administer TENS directly over the site of experimentally induced cold pain because the hand is immersed in water, although investigators did attempt to direct TENS paraesthesia into the painful hand by careful placement over the median nerve at the wrist. Similarly, in ischaemic pain studies TENS was administered over large nerve bundles immediately proximal to the site of pain, at Erb's point, because the upper arm was inaccessible due to the sphygmomanometer cuff. Interestingly, two of the three studies that were able to produce TENS paraesthesia within the site of pain were judged as positive outcome [36,61]. However, only de Tommaso *et al.* [37] were able to demonstrate frequency-dependent effects when TENS was administered at a strong but comfortable intensity and therefore variations in the site of TENS application are unlikely to contribute to the lack of frequency-dependent effects observed in our review. Nevertheless, it is important to recognise that TENS is often given inappropriately in clinical trials and this has led to under-dosing and has influenced the outcomes of randomised controlled trials and systematic reviews [23].

Other methodological issues for TENS studies include difficulties in blinding and randomisation, which have been described in depth elsewhere [61]. Nine of the 13 experimental reports stated that they used a double-blind approach ([33–35] (two studies in one report), [32,36,38,43–44]), although it is unlikely that the subjects were truly blind because they will experience differences in the quality of TENS-induced paraesthesia between the pulse frequency groups. Only one study report did not explicitly state that

subjects were randomly allocated into groups [42]. However, study reports often lacked detail about operational procedures. It is likely that block randomisation was used in many studies because treatment groups often contained equal numbers of participants. Inadequate blinding and randomisation may exaggerate treatment effects by up to 17% and 40%, respectively [62]. We believe that these shortcomings are likely to have less impact on study outcome than the problems associated with inadequate sample size and assay sensitivity, especially as most studies failed to detect differences between groups.

The relevance of experimental pain to the clinical situation has been challenged [47]. Experimental pain is usually evoked using non-injurious stimuli which activate the nociceptive pathway and can be terminated at the request of the participant. In contrast, clinical pain is a more complex biopsychosocial phenomenon which cannot be terminated at will. Clinical pain may occur in the absence of a clearly defined stimulus and often presents with hyperalgesia and/or allodynia resulting from peripheral and central sensitisation of the nociceptive system. Despite these differences, experimental studies are very useful in solving methodological difficulties often encountered in clinical trials. Analgesic drugs reduce clinical and experimental pain to similar levels, suggesting a role for experimental pain studies to inform dosage, toxicity and adverse event profiles before undertaking clinical studies [63]. However, our review demonstrates the importance of designing experimental studies with the same rigour as seen for randomised controlled clinical trials when they are being used as analgesic assays to evaluate treatment interventions.

In summary, claims about optimal TENS settings are based on studies that often fail to isolate the effects of single TENS parameters. Available evidence from experimental studies on healthy human participants does not support the belief that pulse frequency is a key determinant of outcome when the intensity of TENS is standardised at a strong but comfortable intensity close to the site of pain. This finding is compromised because of major shortcomings in study methodologies, including inadequate sample sizes and concerns about the sensitivities of the analgesic assays. For this reason our review should serve to emphasise the need for better research and should not be used as a review of good studies done to date. We intend, in the future, to conduct a similar review which evaluates the effect of intensity when all other TENS parameters are standardised.

Conflict of interest: None.

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