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A Comparison of the Hypoalgesic Effects of Transcutaneous Electrical Nerve Stimulation (TENS) and Non-invasive Interactive Neurostimulation (InterX®) on Experimentally Induced Blunt Pressure Pain Using Healthy Human Volunteers

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Objectives: Non-invasive interactive neurostimulation (InterX®) delivers high amplitude electrical pulsed currents at points of low impedance on the skin. This study compared the hypoalgesic effect of non-invasive interactive neurostimulation with transcutaneous electrical nerve stimulation (TENS).

Materials and Methods: A repeated measures parallel group study on healthy human volunteers randomized to receive strong non-painful TENS or non-invasive interactive neurostimulation for 21 min on the forearm ($N = 10$/group). Pressure algometry was used to determine blunt pressure pain threshold at baseline, 10, and 20 min during stimulation, and 5 min post stimulation.

Results: Low impedance sites were found in half of the participants receiving non-invasive interactive neurostimulation. ANOVA found no effects for intervention ($p = 0.923$), time × intervention interaction ($p = 0.21$), or time ($p = 0.094$).

Conclusions: Given the limited power of this study, we show that there were no significant differences in hypoalgesia between non-invasive interactive neurostimulation and TENS. Unlike our previous studies we also failed to detect a change pain threshold during TENS. Nevertheless, our findings can be used to inform the design of an appropriately powered study on pain patients.

keywords: Hypoalgesia, non-invasive interactive neurostimulation (InterX®), non-therapeutic human experimentation, pain threshold, transcutaneous electrical nerve stimulation (TENS)

Conflict of Interest: Professor Mark I. Johnson has delivered study days on TENS that have been sponsored by pharmaceutical and TENS companies. Professor Deirdre Walsh and Ms. Nicola Biggs declare no conflicts of interest with this study.

INTRODUCTION

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique that is used throughout the world to manage painful conditions, although there continues to be uncertainty about efficacy and effectiveness (1,2). During TENS, electrical pulsed currents are generated by a portable battery powered device and delivered through the intact surface of the skin by self-adhering electrodes. The purpose of TENS is to selectively activate low threshold peripheral afferents as this has been shown to inhibit ongoing transmission of nociceptive input in the spinal cord, leading to pain relief. A strong yet non-painful TENS sensation within the site of pain is a pre-requisite for success (3). A variety of TENS-like devices, that differ in design to a standard TENS device, are available to the general public without prescription although there is very little research on mechanisms, efficacy, and effectiveness. In general, manufacturers overstate the efficacy of these TENS-like devices (4,5).

Non-invasive interactive neurostimulation is a relatively new TENS-like device and is sold under the trade name InterX®. Manufacturers claim that non-invasive interactive neurostimulation relieves pain and promotes healing of various injuries (6). All three randomized controlled clinical trials published to date have demonstrated superiority for non-invasive interactive neurostimulation over placebo (i.e., a no current sham device) for knee osteoarthritis (7), postoperative recovery from bone fractures (8) and operative reduction and internal fixation of bimalleolar, AO type B2 ankle fractures (9).

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Manufacturers claim that the waveform used in non-invasive interactive neurostimulation devices is impedance sensitive and can detect changes in the electrical properties of tissue that alter in response to injury and trauma (6). This is based on the premise that areas of low impedance are optimal sites for electrical stimulation because they correspond to areas of skin associated with myofascial trigger points, acupuncture points, and neural endings (10–13). Treatment protocols involve scanning the skin for areas of low impedance by moving the electrode head of the non-invasive interactive neurostimulation device across the surface of the skin. Points of low impedance are then stimulated by delivering high amplitude electrical currents with pulsed, damped, biphasic, sinusoidal waveforms. During stimulation, the sinusoidal waveform alters in its characteristics according to changes in skin impedance and the tissue status. The electrode head provides feedback about skin impedance so that there can be continual adjustment of the shape of the electrical current in response to any changes in skin impedance and the tissue status. This impedance sensitive interactive waveform used during non-invasive interactive neurostimulation appears to be the unique selling point of the technology and it is suggested that this should confer superiority over standard TENS devices. Interestingly, non-invasive interactive neurostimulation delivers currents to generate a strong non-painful paresthesia in much the same way as that recommended for conventional TENS so there is likely to be some similarity in physiologic mechanisms.

Pre-clinical testing of new treatments in healthy volunteers is critical to ensure safety, efficacy, and optimal dose and technique (14). It is often neglected for non-invasive electrical stimulation techniques because they are not subject to the same regulatory requirements as drug medication and invasive treatments. Pre-clinical research on non-invasive interactive neurostimulation is limited and is available as conference abstracts (15–17). Gilbey et al. (17) have previously shown that ten minutes of non-invasive interactive neurostimulation produced a significant elevation in pressure pain threshold at the forearm in healthy volunteers when compared with a placebo (no current) device. Whether the hypoalgesic effects of non-invasive interactive neurostimulation differ from TENS is not known. The aim of this study was to compare the effects of non-invasive interactive neurostimulation with TENS on pressure pain threshold in healthy human participants. We hypothesized that there would be a difference in pressure pain threshold between non-invasive interactive neurostimulation and TENS at 20 min of stimulation. We did not pre-empt the direction of this difference.

MATERIALS AND METHODS

A repeated measures parallel group study was designed to measure experimentally induced blunt pressure pain thresholds during TENS and non-invasive interactive neurostimulation in pain-free healthy human volunteers. Informed consent was obtained from all participants and the study was approved by the Research Ethics Sub-Committee of Leeds Metropolitan University.

Participants, Recruitment, and Selection

Twenty unpaid healthy human volunteers were recruited by announcements throughout the University. Interested individuals were verbally briefed about the nature of the study and provided with a participant information sheet. Volunteers were given 48 hours before being formally invited to take part in the study. Each participant took part in one experiment. Before the start of the experiment they were screened for study eligibility (18 years or older with no previous use of TENS or TENS-like devices) and contraindications to TENS in line with current professional standards (18). Contraindications included any existing medical condition such as peripheral vascular abnormalities, hypertension and hypotension, peripheral neuropathies, and recent trauma. TENS action depends on normally functioning nerves in the skin so normal skin sensation was an inclusion criterion. Volunteers who were taking any medication or who were likely to take any medication during the period of study were excluded. Participants signed written consent before the experiment and were reminded that they could withdraw at any time without any reason.

Procedure

Each experiment was conducted in a physiology laboratory and facilitated by the principal investigator (NB). Participants were seated throughout the experiment with their non-dominant forearm resting on a side table and instructions delivered verbally, using a series of cue cards. Participants received either strong non-painful TENS or strong non-painful non-invasive interactive neurostimulation. Block randomization was used to ensure equal numbers of participants in each group ($N = 10$ per group) and operationalized using random numbers generated by a computer that were placed in opaque sealed envelopes, which were labeled sequentially for each experiment by a person independent to the study. Pain threshold measurements were taken at baseline, during stimulation at 10 min and 20 min, and 5 min after the stimulator had been switched off (Fig. 1).

Pressure Algometry

Mechanical pain thresholds to blunt pressure stimuli were measured using a Somedic Type II pressure algometer with a flat circular probe (1 cm^2) (Somedic, Horby, Sweden) on the non-dominant forearm, over the flexor carpi radialis muscle using similar techniques to previous studies (19) (Fig. 2a,b). This flexor carpi radialis muscle was chosen because muscle bellies of the forearm have been shown to provide reliable blunt pressure pain measures (20,21). During each test, participants sat with their forearm on a side table and pronated with shoulder abduction approximately 30° and elbow flexion 90°. Measurements were taken at the midpoint between the position of TENS electrodes for TENS or at the equivalent location for non-invasive interactive neurostimulation. Two pain threshold measurements were recorded during one minute with each measure taking no more than 30 sec and the average of the two measurements used for the statistical analysis. During each measurement the head of the algometer probe was placed perpendicular to the skin and pressed at a rate of approximately 50 KPa/sec. Participants were asked to concentrate on forearm sensations until

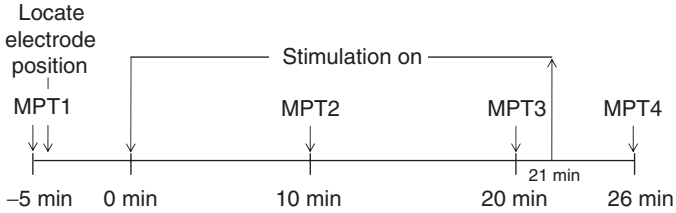

Figure 1. Experimental procedure. MPT, mechanical pain threshold.

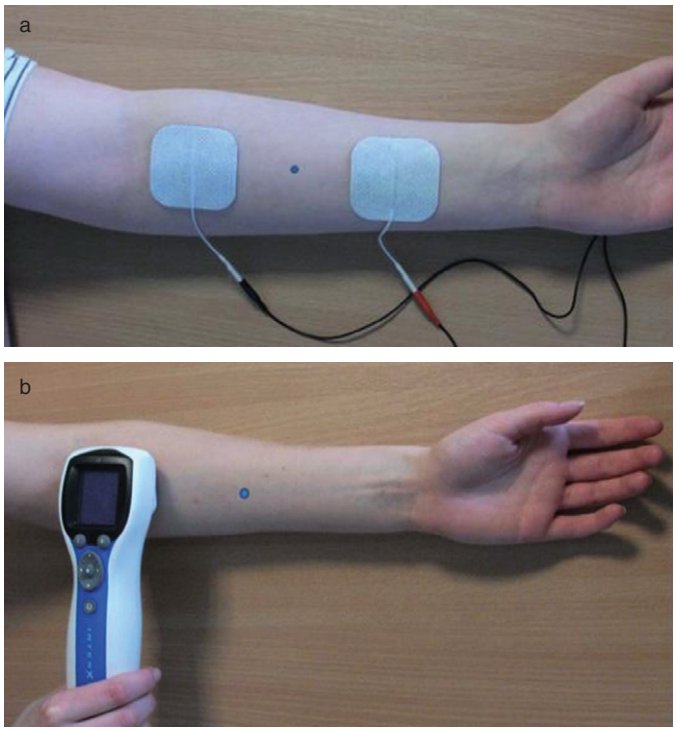

Figure 2. Application of non-invasive interactive neurostimulation (a) and transcutaneous electrical nerve stimulation (b). The small circle marks the location of measurement of mechanical pain threshold.

the force from the pressure probe became definitely painful, at which point they should state "Pain!" and the investigator would immediately withdraw the probe from the skin. The maximum force (KPa) was displayed on the algometer and taken as pain threshold. Verbal instructions were given to participants 30 sec before any action by the principal investigator reading from a cue card.

Interventions

Transcutaneous electrical nerve stimulation and non-invasive interactive neurostimulation were administered for a total of 21 min. Participants were told in pre-study information that there were different types of TENS devices and that some produced a sensation and others did not.

Transcutaneous electrical nerve stimulation was administered so that stimulation covered the median nerve and the flexor carpi radialis muscle using a ProTENS (Nidd Valley) and two square self-adhering electrodes (each 5 × 5 cm, Acupad Multistick TENS Electrodes, Nidd Valley Medical, Knaresborough, UK) using a continuous pulse pattern, a pulse frequency of 150 pulses per second, and a pulse width (duration) of 220 μsec. The proximal electrode was applied to the lateral epicondyle of the elbow, and the leading edge of the distal electrode placed 3 cm below the proximal electrode along an imaginary line between the lateral epicondyle and the midpoint of the wrist creases (see Fig. 2). These settings were chosen because they were as close as possible to the settings used during non-invasive interactive neurostimulation. Participants were instructed to increase the intensity of TENS to achieve a strong non-painful sensation (electrical paresthesia) and reminded to adjust the intensity to maintain this level 5 and 15 min after TENS had been switched on.

Non-invasive interactive neurostimulation was administered using an InterX 5002 device (InterX, Neuro Resource Group, Plano, TX, USA, Fig. 2) following guidance provided in the user manual. The device was preprogrammed to administer currents at a frequency of 180 Hz with pulse duration varying according to current amplitude (range 10–500 μsec). The site of stimulation was determined by using the non-invasive interactive neurostimulation device to scan the forearm for an area of low impedance. If one could not be found after two minutes, non-invasive interactive neurostimulation was administered at the same site as the proximal TENS electrode so that stimulation covered the median nerve and the flexor carpi radialis muscle. The treatment head of the non-invasive interactive neurostimulation device remained stationary during stimulation. The intensity of non-invasive interactive neurostimulation was set at a strong non-painful sensation (electrical paresthesia) and adjusted to maintain this level 5 and 15 min after non-invasive interactive neurostimulation had been switched on.

The current amplitude to achieve a strong non-painful sensation for TENS and non-invasive interactive neurostimulation was recorded after the device was switched on, immediately after measurement of the pre-intervention pain thresholds and again at 6, 12, and 18 min. Current amplitude was taken from the screen display of the non-invasive interactive neurostimulation device and using a Type 4000 Frye Analyser (RDG Medical Ltd, Croydon, UK) during TENS.

Data Analysis

An unpaired *t*-test (two-tailed) was used to analyze the main outcome taken as the difference between the interventions at 20 min of stimulation (i.e., the second during stimulation time point just prior to completion of the "treatment" intervention). Sample size estimate was based on detecting a meaningful difference of 100 KPa using a standard deviation of 75 KPa based on the findings of a previous study by Cowan et al. (22). In addition, repeated measures ANOVA on raw data was used to determine the effect of time within subjects (four levels: baseline, after 10 min of stimulation, at 20 min of stimulation, and 5 min after the end of stimulation) and intervention between subjects (two levels: TENS and non-invasive interactive neurostimulation) on mechanical pain threshold. If Mauchly's test of Sphericity was not assumed then a Greenhouse-Geisser correction was used for the data set. Alpha was set at 0.05, beta at 0.2 (i.e. power of 0.8), and adjustment made for multiple comparisons using the Bonferroni correction.

RESULTS

Twenty healthy volunteers expressed interest in the study and all started and completed the experimental session (14 female, mean [SD] age = 20.7 [0.80] years). Pre-intervention pressure pain thresholds were of a similar magnitude to those reported in previous studies (Table 1 [19,23,24]).

There was no difference between interventions at 20 min of stimulation (mean [SD] difference = 21.0 [16.4] KPa, $p = 0.88$, unpaired *t*-test, power = 0.772). Repeated measures ANOVA found no within-subject effects for time ($F = 2.238$, $p = 0.094$), or time × intervention interaction ($F = 1.55$, $p = 0.21$). There were no between-subject effects for intervention ($F = 0.010$, $p = 0.923$). Visual inspection of the trajectories of each individual across the time course of the experiment revealed no obvious trends in the data (Fig. 3). It was noteworthy that the pain threshold of one participant decreased by half between baseline and the ten minute time point. Repeating the statistical analysis with this participant's data omitted had negli-

Table 1. Mean (SD) Pressure Pain Thresholds (KPa).

	Baseline	10 min of stimulation	20 min of stimulation	5 min after stimulation
Transcutaneous electrical nerve stimulation	699.85 (246.60)	665.50 (264.76)	715.75 (299.25)	715.35 (254.08)
Neurostimulation	783.00 (349.03)	666.40 (314.11)	736.75 (315.65)	657.55 (185.53)

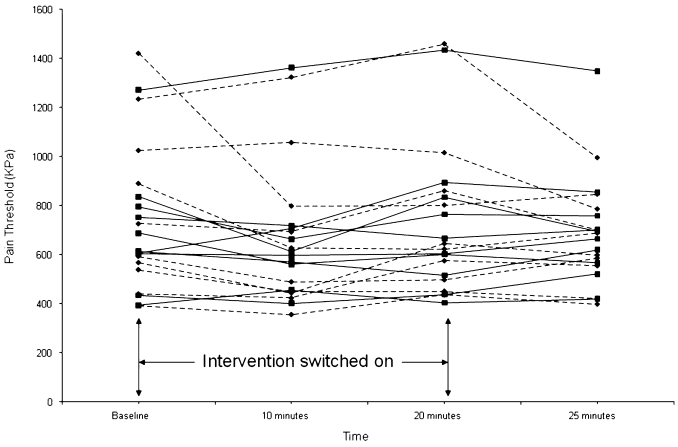

Figure 3. Participant trajectories across the time course of the experiment (dashed line = non-invasive interactive neurostimulation; sold line = transcutaneous electrical nerve stimulation).

gible effect on the findings (repeated measures ANOVA time $F = 2.225$, $p = 0.096$; intervention $F = 0.018$, $p = 0.894$; time × intervention interaction $F = 1.253$, $p = 0.30$).

An area of low impedance was found while scanning with the non-invasive interactive neurostimulation device in five of the ten participants. The mean current amplitude to achieve a strong non-painful sensation over the 21-min intervention was lower for TENS (mean [SD] = 14.05 [7.09] mA) compared with non-invasive interactive neurostimulation (mean [SD] = 23.25 [7.70] mA, mean difference = –9.2 [95% CI = –16.19, –2.21 mA], $p < 0.013$, unpaired *t*-test, Table 2). There were no differences between TENS and non-invasive interactive neurostimulation in the change in current amplitude necessary to maintain a strong non-painful sensation from baseline to 18 min (mean [SD] TENS = 4.0 [2.49] mA, non-invasive interactive neurostimulation = 1.50 [4.33] mA, $p = 0.14$, unpaired *t*-test).

DISCUSSION

This study failed to detect any significant differences between non-invasive interactive neurostimulation and TENS on pressure pain threshold at the flexor carpi radialis muscle in 20 healthy human participants. A higher current amplitude was necessary to achieve a strong non-painful sensation for non-invasive interactive neurostimulation than TENS. Areas of low impedance could only be found in half of the participants receiving non-invasive interactive neurostimulation.

Our study was designed to evaluate the relative efficacy of TENS with non-invasive interactive neurostimulation, so we did not include a placebo control group. Placebo controlled studies have consistently shown that TENS elevates pain pressure pain threshold when administered at a strong non-painful intensity at the site of pain following a similar time course as observed in the present study (19,22–29). Recently, Gilbey et al. (17) conducted an investigation into the hypoalgesic effects of non-invasive interactive neurostimulation, although this is yet to be published as a full report. They found that there was a significant elevation in pressure pain threshold at the forearm in 12 healthy volunteers after a ten-minute non-invasive interactive neurostimulation intervention when compared with a placebo (no current) device. This effect had disappeared 30 min after stimulation.

We found no difference in pain threshold between non-invasive interactive neurostimulation and TENS. One reason may be that the mechanism of action of TENS and non-invasive interactive neurostimulation are similar. Both modalities generate a strong non-painful sensation indicative of low threshold afferent activity and this has been shown to inhibit ongoing transmission of nociceptive input within the spinal cord (2,30,31). Pyne-Geithman and Clark (16) have reported that InterX generated significantly greater physiologic responses than TENS in markers of respiration, lymphocyte metabolism, and cytokine production although it appeared that there were only four participants from the information provided in the abstract.

We found that higher current amplitude was necessary to achieve a strong non-painful sensation for non-invasive interactive neurostimulation compared with TENS. However, current amplitudes to achieve a strong non-painful TENS sensation were lower than previous studies by ourselves (32) and others (33), which tend to be between 18 and 25 mA. Lower than expected values may be because the participants in the TENS group did not increase TENS intensity to the appropriate level, despite clear instructions. This seems unlikely because we would expect to see a similar effect for participants in the non-invasive interactive neurostimulation group who received similar instructions to TENS participants. Methods of measuring current amplitude differed with TENS amplitudes measured using a Type 4000 Frye Analyser and non-invasive interactive neurostimulation within the non-invasive interactive neurostimulation device itself. Current amplitudes for TENS were above magnitudes previously reported for sensory detection threshold so we are confident that participants were experiencing TENS sensations.

Higher current amplitudes for non-invasive interactive neurostimulation may be due to a lack of a conductive medium used at the electrode–skin interface. Non-invasive interactive neurostimulation delivers current using a single electrode head that is made of concentric stainless steel outer and inner electrodes. These stainless steel electrodes make direct contact with the skin without the use of electrode gels. If the impedance at the interface between electrode and skin remains high, it will hinder the passage of electrical currents across the electrode–skin interface. This may generate areas of high current density (termed hot spots) resulting in skin irritation (34), although we observed no skin irritation in the present study. For most transcutaneous electrical stimulating devices gels are used to reduce the large impedance of the stratum corneum improving electrical contact between the electrode and the skin. Manufacturers claim that the waveform used during non-invasive interactive

Table 2. Mean (SD) Current Amplitude (mA).

	Baseline	6 min of stimulation	12 min of stimulation	18 min of stimulation	Mean	Increase over 18 min
Transcutaneous electrical nerve stimulation	11.6 (5.87)	13.2 (7.19)	15.4 (7.83)	16.0 (7.77)	14.05 (7.09)	4.0 (2.49)
Neurostimulation	22.7 (6.77)	22.7 (7.13)	23.4 (8.19)	24.2 (9.25)	23.25 (7.70)	1.50 (4.33)

neurostimulation changes its characteristics in response to ongoing changes in skin impedance and that this facilitates delivery of currents through the skin, negating the need for conductive gel. Further research into the effect of the dynamic waveform used during non-invasive interactive neurostimulation on the skin-electrode interface is needed.

The non-invasive interactive neurostimulation device only identified areas of low impedance in five of the ten participants. It is claimed that peripheral nerve stimulation techniques should be administered over skin with low impedance (13), although recent studies have shown an inverse relationship between impedance measurements and current thresholds to activate nerves percutaneously (35). Research has suggested that areas of low impedance correspond to myofascial trigger points, acupuncture points, and where nerve branches course close to the skin surface (10–12), although recent studies have found that acupuncture points may correspond to areas of high or low impedance (36,37). Clearly, much more research is needed to characterize low impedance points on the skin including their distribution in healthy individuals and patients with disease including pain, and whether these points alter in size and distribution over time.

All three randomized controlled clinical trials conducted on the pain relieving effects of non-invasive interactive neurostimulation have been positive. Selfe et al. (7) found that non-invasive interactive neurostimulation scored better than a sham (no current) device for SF-36 Vitality scale and patient global assessment, but not pain, in 37 patients with knee osteoarthritis. Gorodetskyi et al. (8) found significantly better pain relief when 60 patients with trochanteric fracture of the femur were treated for ten days with a non-invasive interactive neurostimulation device compared with a sham device. In a follow-up study they reported similar findings for 60 patients after operative reduction and internal fixation of bimalleolar, AO type B2 ankle fractures with comminution (9). Patients received normal post-operative care in addition to interventions and it was found that those in the non-invasive interactive neurostimulation group used less medication when compared with the sham group. It was claimed that patients were blind to treatment allocation. However, as the active non-invasive interactive neurostimulation generated a strong sensation of electrical paresthesia and sham stimulation (no current) did not, it is possible that patients could guess which treatment was active, biasing outcome in favor of the active groups.

Study Limitations

The possibility of a type 2 error cannot be discounted in this study. We were interested in interaction effects although these can be associated with low power. The observed power for interaction effects in our study was only 0.354, despite using sample sizes similar to analyses to detect differences between TENS and placebo in previous studies. It is possible that a smaller magnitude of difference, and a larger sample size, is needed to determine relative efficacy of two active interventions. Nevertheless, the observed power of the *t*-test used for our main outcome was 0.77 and for time was 0.813 so we feel relatively confident that the lack of difference was not due to our statistical method. However, we cannot discount the possibility that variability introduced during the execution of the study may have masked effects. The omission of a placebo group did not enable us to explore this variability further, and a placebo group should be included in future studies. Another limitation may have been a massage-like effect created by pressing the electrode head of non-invasive interactive neurostimulation on the surface of the skin during stimulation. This may have increased hypoalgesia.

The generalizability of our results may be limited. Our recruitment strategy focused on university students and staff rather than a general population-based sample. We used a single sensory modality testing procedure (i.e., blunt pressure pain) and did not assess other modalities of nociception (i.e., thermal and electrical) that can be captured using a multimodal testing procedure in order to characterize the complexity of pain experience (38). Also, there are fundamental differences between non-injurious pain in an experimental setting and clinical pain driven by pathological processes (14). Noxious input resulting from pressure algometry as used in the present study results from transient activation of A-delta (and possibly C-fiber) mechanosensitive nociceptors, although the final pain experienced also will involve activity in low threshold non-noxious A-beta mechanoreceptive fibers. Unlike clinical pain the duration of our experimentally induced pressure pain was short-lived, with minimal tissue injury and no peripheral or central sensitization. For these reasons we would recommend a large-scale clinical trial.

CONCLUSION

In conclusion, we detected no significant differences in the hypoalgesic effects between non-invasive interactive neurostimulation and TENS on pressure pain thresholds in healthy volunteers, although the possibility of a type 2 error cannot be discounted. Despite the positive outcome of clinical trials, our findings raise uncertainty about the process of monitoring and subsequently stimulating areas of low skin impedance. Our study findings should act as a catalyst for further research from basic and clinical sciences.

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Authorship Statements

All authors contributed to the design, data analysis, and preparation of the manuscript including intellectual input at all stages. Ms. Biggs

and Professor Johnson conducted participant recruitment and data collection. All authors approved the final manuscript. The Faculty of Health and Social Sciences at Leeds Metropolitan University provided funding for the study. All authors had complete access to the study data.

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COMMENTS

This is an important comparative study that evaluates effects of the non-invasive neurostimulation approaches. The authors discovered that traditional transcutaneous electrical nerve stimulation (TENS) and "noninvasive interactive neurostimulation" are very similar in terms of producing hypoalgesia.

The study is simple but well documented. However, the findings in healthy volunteers may not be completely transferable to pain patients and therefore I would encourage the authors to perform similar comparisons in symptomatic patients as the results may be either concordant with those in healthy controls—or completely surprising in terms of discovered difference between two modalities.

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In this study, this group of investigators compared the effects of two techniques of peripheral electrical stimulation (neurostimulation (Inter®X) vs. transcutaneous electrical nerve stimulation (TENS)) on pain threshold.

Though ANOVA showed no significant effects for intervention, time and time x intervention interaction, this study was powered only to detect large differences between groups (effect sizes larger than 1) and in addition it is important to note that this study found no significant effect also for TENS. Thus reader should be aware of these issues when analyzing results from this study.

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Every day we read advertisements about new medical devices. A majority of them are promising non-invasive and effective cure of illnesses, or at least faster and better relief of suffering. Not surprisingly, new devices are usually more expensive and have more attractive design. However, the latest is not necessarily the greatest. This study failed to show superiority of a new brand-name device versus our old friend TENS.

The study was conducted in a clean unbiased experimental setting. However, pressure-induced pain in healthy volunteers and its alleviation by TENS or other devices may not represent pathological conditions with altered pain perception, modulation and transmission. Clinical comparative studies should be conducted to support or dismiss advantages of new methods.

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Comments not included in the Early View version of this paper.

