An investigation of the development of analgesic tolerance to TENS in humans

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ABSTRACT

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive modality used to control pain. Animal models show that repeated TENS application produces analgesic tolerance and cross-tolerance at spinal opioid receptors. The aim of the present investigation was to examine whether repeated application of TENS produces analgesic tolerance in humans. One hundred healthy subjects were randomly assigned to 1 of 4 groups: control, placebo, low-frequency (4 Hz) or high-frequency (100 Hz) TENS. TENS was applied daily for 5 days to the nondominant upper limb; pressure-pain threshold (PPT) measurements were recorded before and after TENS. Temporal summation to mechanical stimulation was recorded on days 1 and 5, before and after TENS. Diffuse noxious inhibitory control (DNIC) was tested on day 5 using the cold pressor test and PPT measurements. There was an initial increase in PPTs in both low- and high-frequency TENS groups when compared with placebo or control groups. However, by day 5 this TENS-induced increase in PPT did not occur, and there was no difference between active TENS and placebo or control groups. High-frequency TENS decreased temporal summation on day 1 when compared with day 5. DNIC increased the PPT similarly in all groups. These data suggest that repeated daily application of TENS results in a decrease in its hypoalgesic effect by the fifth day and that the tolerance-like effect to repeated TENS results from tolerance at centrally located opioid receptors. The lack of change in DNIC response suggests that TENS and DNIC utilize separate pathways to produce analgesia.

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1. Introduction

Transcutaneous electrical nerve stimulation (TENS) involves the application of electrical currents to the skin for pain control; it is a noninvasive modality that is commonly used by health care professionals to control both acute and chronic pain arising from several conditions [3,18,20,24,49,52,53]. TENS emerged and became widely accepted after the publication of the gate control theory of pain [44]. Both high- and low-frequency TENS cause hypoalgesia through the release of endogenous opioids in the central nervous system [9,34,58]. At the spinal level and the rostral ventral medulla, there are different opioids released with different stimulation frequencies and thus different opioid receptors activated to produce analgesia with high- or low-frequency TENS [62]. Low frequencies, usually below 10 Hz, activate μ-opioid receptors, and high frequencies, above 50 Hz, activate δ-opioid receptors [9,34,58].

Repeated stimulation of opioid receptors by repeated administration of morphine or opioid analgesics can lead to an analgesic tolerance, defined as a decrease in analgesic effectiveness with repeated use [43]. In a similar way, repeated utilization of therapeutic electrophysical agents that reduce pain through release of endogenous opioids could have a gradual diminution of their analgesic effect. Chandran and Sluka [9] demonstrated in rats that repeated administration of low- and high-frequency TENS leads to a development of opioid tolerance with a corresponding cross-tolerance to intrathecally administered μ- and δ-opioid agonists, respectively. In clinical practice, TENS is usually applied daily over many weeks. Approximately 30% of patients fail to respond to TENS and, of the patients who respond initially, only one third continue to obtain pain relief after 2 years [4]. Solomon et al. [63] showed that people who had been taking opioids long enough to develop tolerance before surgery did not respond to TENS when used postoperatively. Although commonly accepted that TENS reduces its efficacy with repeated application, the development of tolerance to TENS has not been investigated and confirmed in human subjects. With these concerns in mind, the aim of the present investigation was to examine the analgesic tolerance to TENS in human subjects.

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2. Methods

2.1. Subjects

A total of 100 healthy, TENS-naïve, pain-free subjects (48 men, 52 women; mean age 31.75 ± 12.05 years; age range 18 to 60 years) were recruited from the staff and students of the University of Iowa after approval was obtained from the local institutional review board. The sample size was calculated using data from previous studies on pressure-pain threshold (PPT) and TENS [51]. Considering a significance level of 5%, power of 80%, 4 treatment groups, and an effect size of 0.4, it was calculated that 25 participants were required in each group. Subjects were screened and excluded if they had altered skin sensation or history of recent trauma in upper limbs, cardiac pacemaker, pregnancy, or if they were receiving any type of pain medication. After the participants provided written informed consent, they were stratified by gender and randomly assigned to 1 of 4 groups: control ($n = 25$), placebo TENS ($n = 25$), low-frequency TENS ($n = 25$), or high-frequency TENS ($n = 25$). Randomization was performed using the sequentially numbered, opaque sealed envelopes allocation concealment method [22,55]. The envelopes were stored in a secure cabinet that only the allocation investigator had access to, and were opened immediately before intervention allocation.

Demographic information, including age, race, gender, height, and weight, were recorded. There were no significant differences between groups based on age, race, gender, or body mass index (Table 1).

2.2. PPT

The PPT has been reported to reflect mainly pressure-pain sensitivity of deeper tissues [36–38]. PPT measurements were recorded by an assessor who was blind to group allocation using a Somedic Type II digital pressure algometer (Somedic Inc., Hörby, Sweden) from 3 marked spots along the extensor mass of the nondominant forearm (2, 3, and 4 cm below the elbow crease) (Fig. 1). The pressure was applied perpendicularly to the skin at a rate of 50 kPa/s through a flat circular probe measuring 1 cm^2 and covered with 1 mm of rubber to avoid painful skin stimuli due to sharp metal edges [37,38]. Subjects were instructed to press the algometer button when pressure was first perceived as pain, and the algometer was retracted at this point. The average of the PPT scores recorded at the 3 points was used as the final value at each measurement time. Each subject had 2 practice trials on the non-testing forearm followed by the data collection round.

2.3. Tonic experimental pressure pain stimulus

Pain intensities to tonic pressure were used to determine pressure temporal summation. A temporal summation (TS) area was
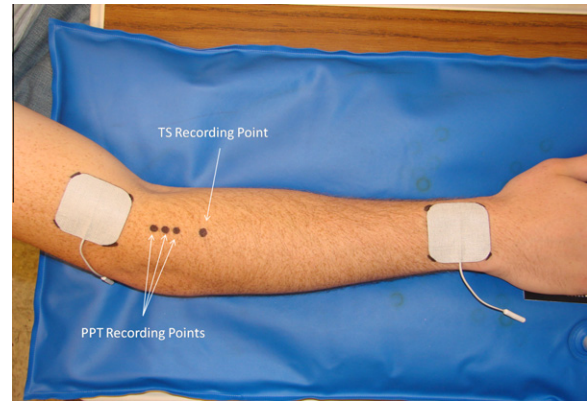
Fig. 1. The placement of transcutaneous electrical nerve stimulation electrodes and recording sites for pressure-pain threshold (PPT) and temporal summation (TS).

marked on the posterior aspect of the nondominant forearm, over the extensor mass, 6 cm below the crease of the elbow (Fig. 1). Temporal summation was measured with a custom-built device incorporating a pressure transducer and a lever with a movable weight to grade the pressure applied (kPa). The forearm was secured in place with a vacuum pillow (Versa Form, Sammons Preston, Bolingbrook, IL), and the pressure stimulus was delivered through a 1-cm^2 probe. Temporal summation was tested at an 8/20 pain rating for 2 min with subjects rating their pain every 10 s on a 0 to 20 numeric rating scale (0 = no pain and 20 = the worst pain imaginable) starting at time 0. The area under the curve was calculated for data analysis using the following formula:

$$A = \sum_{i=1}^{12} (P_i - P_0) * \Delta t$$

where A, area under the curve; P_i, pain intensity at moment i; P_0, pain intensity at moment 0; Δt, time frame between the measurements of pain intensity (10 s).

The 0-to-20 numeric rating scale was used because it was found to be easier to use and associated with higher compliance and lower failure rates when compared with the Visual Analogue Scale [28]. It has established validity and reliability for assessing acute pain [23,30,46].

2.4. TENS procedure

The subject's skin was cleansed with mild soap and water, and 2 square self-adhesive electrodes (5 × 5 cm) (StimCare Premium Electrodes, Empi Inc., St. Paul, MN) were placed 1 cm proximal to the elbow crease and 1 cm proximal to the wrist crease on the dorsum of the nondominant upper limb. The corners of the electrodes were marked on the skin using a permanent marker to allow exactly the same electrodes positioning during the 5 consecutive

Table 1
Characteristics of the study participants.

	Control ($n = 25$)	Placebo TENS ($n = 25$)	Low-frequency TENS ($n = 25$)	High-frequency TENS ($n = 25$)
Gender				
Male	12 (48%)	12 (48%)	12 (48%)	12 (48%)
Female	13 (52%)	13 (52%)	13 (52%)	13 (52%)
Age (mean ± SD)	30.48 ± 2.04	30.4 ± 2.53	38.2 ± 2.85	27.92 ± 1.67
BMI (mean ± SD)	25.21 ± 0.92	26.16 ± 0.62	25.46 ± 1.09	25.59 ± 1.09
Race				
Caucasian	21 (84%)	24 (96%)	21 (84%)	22 (88%)
African American	1 (4%)	0 (0%)	0 (0%)	1 (4%)
Asian	1 (4%)	1 (4%)	3 (12%)	1 (4%)
Other	2 (8%)	0 (0%)	1 (4%)	1 (4%)

BMI, body mass index; TENS, transcutaneous electrical nerve stimulation.

days of the study (Fig. 1). Subjects were instructed not to wash off these markings during the week of testing.

Two active units were used: one was set at low frequency (4 Hz) and another was set at high frequency (100 Hz). These active units applied TENS (100-μs pulse duration) at maximal tolerable intensity for 20 min to the nondominant forearm, daily for 5 days. This duration of TENS application was based on other studies showing the effect of TENS in experimental pain models [10–12,51,72]. Maximal tolerable intensity was the greatest intensity the subject could tolerate that was not painful. In some cases this intensity produced a motor contraction. The average amplitude used in the low-frequency TENS group was 30.64 ± 1.59 mA and in the high-frequency TENS group was 25.79 ± 1.29 mA. Previous work from our laboratory in animals shows that TENS activates large-diameter afferents at just below or just above motor threshold. Nociceptors were not activated until we got to 2 times motor threshold, a clearly painful stimulus in humans [50]. In humans, a similar pattern of activation is observed in the ranges that we used. Levin and Hui-Chan [41] performed recordings from the median nerve in human subjects and showed that high-frequency TENS (100 Hz) applied at 3 times the sensory threshold activates only large-diameter Aβ fibers. Similarly, low-frequency TENS (4 Hz), at maximal tolerable intensity, activates only Aβ afferent fibers, whereas Aδ activation only occurs at intensities above maximal tolerable intensity. Thus, we believe that the intensities we used in the present study only activated Aβ afferent fibers. The pulse amplitude applied on day 1 was noted, and on all subsequent days the same dose of TENS was applied, i.e., all TENS parameters were kept constant for the rest of the week. The placebo TENS was applied using a sham unit that looked similar to the active unit. This unit actively applied TENS (continuous mode, 100 Hz, 100 μs) at maximal tolerable intensity for 30 s, and then the current ramped off over the next 15 s. The same parameters used on day 1 were used for the rest of the week. All devices were Rehabilicare Maxima TENS units, and they were identical in appearance (Empi Inc., St. Paul, MN). They delivered a rectangular, balanced, asymmetrical, biphasic pulsed current.

The TENS units were calibrated using a digital oscilloscope (TDS 430A, Tektronix Inc., Beaverton, OR) before starting the study. For each pulse amplitude setting on the devices, peak-to-peak voltage was measured across a 1-kΩ resistor to calculate the corresponding current in mA.

TENS applications were performed by an investigator who did not participate in outcome assessments. During the pain measurements, the intensity of TENS was decreased and kept at a sensory intensity level to ensure the pain assessor was kept blind to the subject's group allocation.

2.5. Activation of diffuse noxious inhibitory control

The cold pressor test was used on day 5 to induce pain and to trigger the diffuse noxious inhibitory control (DNIC) response [35,65]. The conditioning stimulus consisted of the immersion of the subjects' testing side lower extremity in a bucket of ice water (4 °C) to just above the ankle. Pain intensity rating was measured 20 s after immersion on a 0-to-20 scale. PPT was recorded 30 s after immersion from the 3 locations over the nondominant forearm as described before. Before they removed the foot from the water, subjects were asked to rate their pain again on a 0-to-20 scale. The percentage of PPT change was calculated considering the PPT values recorded on day 5 (baseline).

2.6. General overview of protocol

One day 1 after obtaining consent and demographic information, the subjects were randomized into 1 of 4 groups. They were asked to remain seated in a comfortable upright position during all procedures. The nondominant forearm was cleansed, the PPT and TS areas were marked as described before, and the TENS electrodes were applied to subjects allocated in active or placebo TENS groups. PPTs were assessed, followed by TS measurement, and the pain assessor left the room. In the placebo TENS, low-frequency TENS, and high-frequency TENS groups, the leads were connected to the electrodes and the treatment was applied for 20 min. Subjects in the control group were informed that they should rest for 20 min. After a 20-min treatment interval, the pain assessor returned, TS and PPTs were reassessed, and the subject's weight and height were measured. On days 2 to 4, PPTs were recorded before and after a 20-min treatment (or rest in control group) interval. On day 5, the PPTs and TS were recorded before and after the 20-min TENS application (or rest in control group). After TENS, the DNIC response was assessed.

2.7. Blinding assessment

At the conclusion of testing, the TENS investigator asked the subject, "Do you think you received active TENS, placebo TENS, or don't know?" The pain assessor was asked "Do you think the subject received active TENS, placebo TENS, or don't know?" Their responses to these questions were recorded and used to gauge the adequacy of subject and investigator blinding [51].

2.8. Statistical analyses

Changes in PPT were calculated each day as percentage of baseline (pre-TENS), where no change was equivalent to 0%. Positive percentage values represent hypoalgesia, and negative values represent hyperalgesia. Changes in temporal summation for pressure stimuli were calculated as a difference in the area under the curve for the duration of testing (i.e., 120 s) post-TENS to pre-TENS. Descriptive statistics were calculated for all variables, and tests for normal distribution (Shapiro–Wilk) were carried out. The PPT percentage change data were normally distributed, and were therefore analyzed using a repeated-measures ANOVA with between-subjects factors. A one-way ANOVA for independent samples compared differences between groups at each time period. Post-hoc testing was performed with a Tukey test for differences between groups. A χ^2 test was used to compare the percentage of summators and nonsummators on days 1 and 5. Repeated-measures ANOVA was also used to compare differences across time during TS, between summators and nonsummators, and between days 1 and 5 for groups. A paired Student t test compared the difference in TS between days 1 and 5 for each group and the pain intensity during DNIC test at 20 s and at the end of test. The PPT percentage of change data recorded during DNIC tests were not normally distributed and were therefore analyzed using a Kruskal–Wallis test. Associations among the pain intensity and percentage of PPT change during DNIC tests were assessed using Pearson's product–moment correlation coefficients. Statistical significance was set at $P < .05$. All analyses were performed using SPSS (version 17.0; SPSS Inc., Chicago, IL). Data are presented as mean ± SEM.

3. Results

3.1. PPT data

Mean PPT percentages of change (±SEM) for all experimental groups on each day are shown in Fig. 2. The repeated-measures ANOVA with between-subjects factors revealed differences over days ($P = .006$) and between groups ($P > .001$). There was no significant interactive effect between days and groups ($P = .091$).
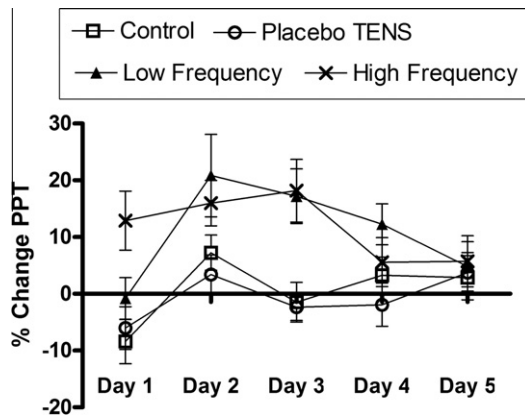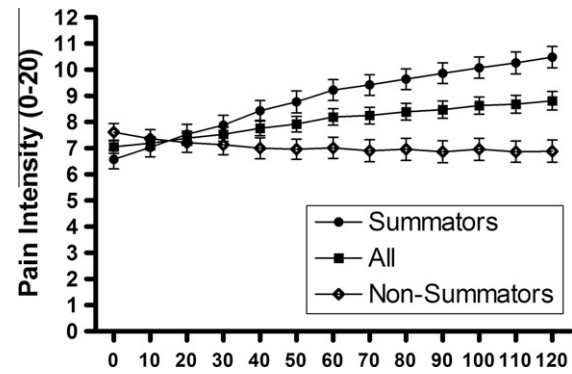
Fig. 2. Percentage of change in pressure-pain threshold (PPT) for each experimental group during the 5 consecutive days. TENS, transcutaneous electrical nerve stimulation.

Fig. 3. Pain intensity during temporal summation to tonic pressure in all subjects, summators, and nonsummators.

Post-hoc Tukey tests indicated a significant hypoalgesic effect in the low-frequency TENS group when compared with the control group ($P = .024$) and the placebo TENS group ($P = .004$). Similarly the high-frequency TENS group showed a significant difference when compared with control and placebo TENS groups ($P = .012$, $P = .002$). No significant differences were found between control and placebo TENS groups ($P = .945$) or between low- and high-frequency TENS groups ($P = .995$).

For comparisons between groups on each day, control and placebo TENS groups were combined because there were no significant differences between them. One-way ANOVA for independent samples identified that significant differences occurred between the combined control and placebo TENS groups and the other experimental groups from day 1 today 4 with values ranging from $P < .0001$ to $P = .0443$. On day 5, no differences were observed between groups ($P = .8766$), representing a decrease in hypoalgesic effect presented by active TENS groups. Post-hoc Tukey tests are summarized in Table 2.

3.2. Mechanical temporal summation data

One subject was excluded from analysis due to a large variation in pressure readings for mechanical temporal summation testing. Fig. 3 shows the pain intensity during temporal summation to tonic pressure in all subjects. There was a significant increase in pain over time ($P < .0001$). Further, the subjects were divided in summators ($n = 53$) and nonsummators ($n = 46$) (summators were defined as having an area under the curve above 100 pain intensity·sec).

There was a significant higher increase in pain intensity over time in summators when compared with nonsummators ($P = .001$). A χ^2 test revealed no significant difference in percentage of summators on day 1 compared with day 5 ($P = .1070$).

When considering all subjects (summators and nonsummators), there were no significant changes in area under the curve before and after TENS on days 1 and 5 ($P > .05$). However, considering only the summators, both the placebo TENS and the high-frequency TENS groups presented a decrease in mechanical temporal summation on day 1 after treatment ($P = .0325$, $P = .0120$) (Fig. 4).

Repeated-measures ANOVA did not show significant differences in the difference scores in the area under the curve (area under the curve after TENS minus area under the curve before TENS) between groups ($P = .072$) and across time ($P = .132$) in summators. Nevertheless, when comparing the difference in the area under the curve on day 1 to day 5, the high-frequency TENS group showed a significant decrease in difference scores ($P = .036$) on day 5 (Fig. 5), suggesting reduced effectiveness of high-frequency TENS on temporal summation.

3.3. DNIC data

As described before, pain intensity was measured during the cold pressor test, 20 s after immersion and at the end of test, on a 0-to-20 scale. The mean pain rating for all subjects at 20 s was 8.95 ± 0.48, and at the end was 12.19 ± 0.50. There was a significant difference in pain intensity between the 2 times ($P < .0001$). There was also a positive correlation between the pain intensity during the cold pressor test and the percentage of change in PPT ($r = .289$, $P = .004$) (Fig. 6). There was no significant difference in

Table 2
Summary of Tukey post-hoc tests for statistical comparison between low- and high-frequency TENS groups with the combined control + placebo TENS groups at each day.

Day	Group	Comparison group	Mean difference between groups	P value
1	Control + placebo	Low frequency	−6.39	>.05
		High Frequency	−20.11	**<.001**
	Low frequency	High frequency	−13.72	>.05
2	Control + placebo	Low frequency	−15.60	**<.05**
		High Frequency	−10.73	>.05
	Low frequency	High frequency	4.86	>.05
3	Control + placebo	Low frequency	−19.13	**<.01**
		High Frequency	−20.10	**<.001**
	Low frequency	High frequency	−0.96	>.05
4	Control + placebo	Low frequency	−11.65	**<.05**
		High Frequency	−4.97	>.05
	Low frequency	High frequency	6.68	>.05
5	Control + placebo	No significant differences		

TENS, transcutaneous electrical nerve stimulation. Bold numbers represent significant P value.
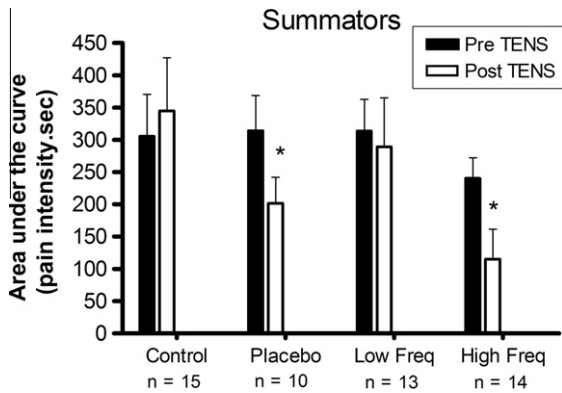
Fig. 4. Area under the curve after temporal summation to tonic pressure in summators subjects on day 1. * Significant difference with the pre-TENS area. TENS, transcutaneous electrical nerve stimulation.

Fig. 6. Scatter plot and correlation between pain intensity and percent change in pressure-pain threshold (PPT) during diffuse noxious inhibitory control test. TENS, transcutaneous electrical nerve stimulation.

the percentage of change in PPT between the study groups ($P = .6858$) (Fig. 7).
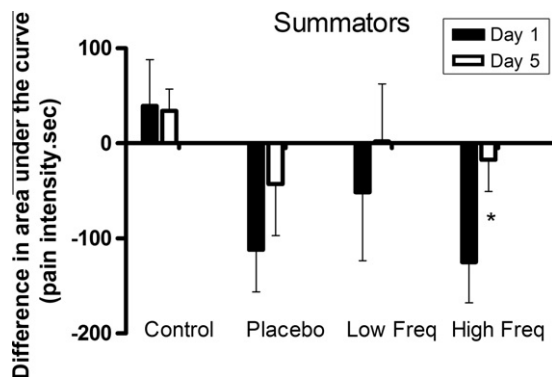
3.4. Assessment of blinding

The pain assessor correctly identified that subjects received an active TENS unit in 4% (1 of 25) of cases in both the high- and low-frequency TENS groups. The same rate was observed in the placebo TENS group, in which the assessor correctly identified the placebo unit in 4% (1 of 25) of the time. In other words, the assessor was blinded 96% of the time when recording pain measures in placebo, low-frequency, and high-frequency TENS groups, indicating successful blinding ($P < .0001$).
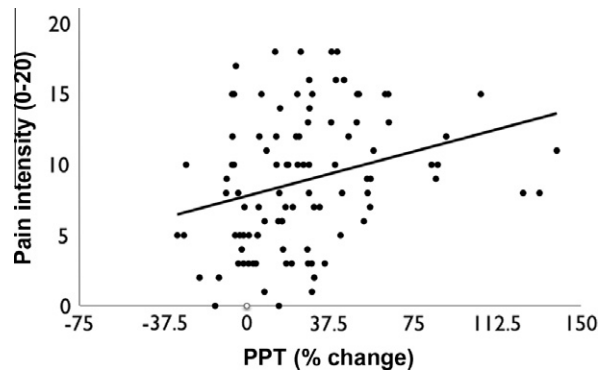
Subjects were blinded to the treatment 20% (5 of 25) of the time in the high-frequency TENS group, 36% (9 of 25) in the low-frequency TENS group, and 48% (12 of 25) in the placebo TENS group. The rate of blinding in the placebo TENS group was no different than chance (random 50:50 probability) ($P = .8415$).

4. Discussion

Patients with chronic pain who initially respond to TENS may become long-term users [8,26,32,33]. Because animal studies show that TENS activates opioids receptors to produce analgesia, repeated TENS applications could cause analgesic tolerance similar to long-term use of opioids [43]. Although analgesic tolerance to TENS has been demonstrated in rats [9,17,19], this is the first study designed to address specifically the analgesic tolerance to TENS in

humans. The results show that repeated daily application of either high- or low-frequency TENS with the same daily dose (intensity, frequency, pulse duration, and treatment duration) and electrode position results in a decrease in its hypoalgesic effect by the fourth and fifth consecutive days, respectively. These data parallel findings in animal studies showing that the tolerance-like effect to repeated TENS results from tolerance at centrally located opioid receptors [9]. Clinical studies in human subjects confirm that opioid receptors play a role in TENS analgesia. These studies show release of endogenous opioids in human subjects during TENS, that low- and high-frequency TENS analgesia is blocked by systemic naloxone, and that TENS is less effective in patients who are opioid tolerant [27,39,40,54,56,63]. Clinically, 32% of long-term users of TENS with a variety of chronic pain conditions report a decline in TENS efficacy from the time the unit was issued [32]. However, the length of TENS utilization necessary to cause analgesic tolerance in these users was not reported. It is possible that in a clinical setting, the development of analgesic tolerance can be delayed if TENS parameters or treatment schedule are changed. We previously [19] showed in rats that mixed-frequency (low and high frequency simultaneously) or daily-alternating-frequency (4/100 Hz) TENS delays the occurrence of analgesic tolerance. Alternatively, increasing the pulse amplitude, and thereby increasing the dose, could also alleviate analgesic tolerance to TENS. Future experiments need to confirm whether changing stimulation parameters in human subjects can prevent analgesic tolerance.

Prior studies compared the efficacy of different frequencies of TENS and mixed TENS frequencies on a variety of outcomes. Alternating TENS frequency (2 Hz, 100 μs, 3.5 s × 100 Hz, 700 μs, 2.5 s) results in a greater increase in heat pain thresholds in healthy subjects when compared with 2 Hz, 100 Hz, or control (no TENS) [64].
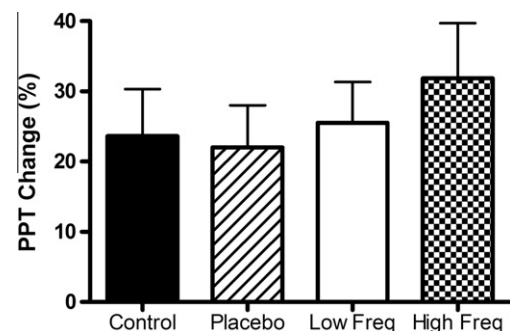

Fig. 5. Difference scores (post-TENS area – pre-TENS area) in area under the curve after temporal summation to tonic pressure in summators subjects on days 1 and 5. * Significant difference with day 1. TENS, transcutaneous electrical nerve stimulation.

Fig. 7. Percentage of change in pressure-pain threshold (PPT) during cold pressor test in all groups. TENS, transcutaneous electrical nerve stimulation.

However, 100-Hz TENS was more effective for increasing the mechanical pain threshold [64]. When comparing different pulse patterns of TENS on ice-pain thresholds in healthy subjects, continuous high-frequency TENS (80 Hz) produced the greatest mean elevation when compared with burst, modulation (burst with amplitude modulation), and random frequencies (14 to 188 Hz), although all pulse patterns increased ice-pain thresholds when compared with controls [31]. In direct contrast, Chen and Johnson [10] found no differences in hypoalgesic effect between constant-frequency TENS (80 Hz) and frequency-modulated TENS, in which the frequency varied from 20 to 100 Hz. It is possible that both applications (constant-frequency and frequency-modulated TENS) activated only high-frequency mechanisms, whereas prior studies activated low-frequency mechanisms [17,19,57–59,61,62]. Unfortunately, few studies have utilized placebo controls for comparison. Although Johnson et al. [31] compared different frequencies against no-treatment controls, Chen and Johnson [10] did not use a control group. The current study showed analgesia with both low-frequency (4 Hz) and high-frequency (100 Hz) TENS when compared with placebo or a no-treatment control group, but no difference between the 2 active TENS groups. However, on day 1, 4 Hz had no effect on PPTs, whereas 100 Hz increased the PPTs. This finding suggests that low-frequency TENS has a delayed hypoalgesic effect when compared with high-frequency TENS. Low-frequency TENS increased the PPT on days 2, 3, and 4, whereas high-frequency TENS increased PPT on days 1, 2, and 3. These results are in accordance with those of other investigators, who compared different TENS frequencies on PPT, performing only 1 treatment session. In these studies, high-frequency TENS was more effective than low-frequency TENS for PPT increase [12,14, 64,69,70]. Animal studies show that high- and low-frequency TENS activate different neuropharmacological mechanisms in the central nervous system [59–61]. Therefore, it is possible that mechanisms activated by high-frequency TENS promote a faster hypoalgesic response than low-frequency TENS in an experimental model.

Increasing intensity of stimulation is another potential mechanism by which we could alleviate tolerance. Prior studies show that low-intensity TENS does not produce analgesia [1,6,13,14,45,52,71], and the intensity of stimulation is correlated with the degree of analgesia [51]. We propose that continuously increasing intensity of stimulation within a single session or daily could increase dose and prevent the development of analgesic tolerance.

The current study used a novel type of sham TENS unit to deliver placebo TENS that has been validated recently [51]. This sham unit applied TENS (100 Hz, 100 µs) at maximal tolerable intensity for 30 s, and then the current ramped off over the next 15 s. The fact that the sham unit delivers electrical current for a short period of time increases the rate of subject blinding [15,51]. This time is considered too brief to have any definite physiological effect [15]. Our success in blinding the pain assessor (96%) was similar to previous studies that used this novel type of TENS placebo [15,51]. The pain assessor correctly identified that subjects were receiving active TENS treatment only once in both high- and low-frequency TENS groups; this was because it was possible to notice mild muscle contractions during PPT recordings in these subjects. The success of subject blinding in the placebo TENS group (48%) is in accordance with results from a previous study (40%) [51]. However, this level of blinding was lower than that observed by Cowan et al. [15] (71%) when using the current intensity at sensory threshold. It is possible that the use of a maximal tolerable intensity in the present study was responsible for this difference, making it easier for the subjects to notice when the current ramped off.

The mechanism of analgesic tolerance is not completely understood, and a number of neurotransmitters and receptors have been described. The neuropeptide cholecystokinin (CCK) has been implicated in the development of tolerance to TENS [17]. CCK is an endogenous opioid antagonist that activates CCK-A and CCK-B receptors [17,74]. Prior work shows that both high- and low-frequency TENS tolerance can be prevented by blockade of CCK-A and CCK-B receptors, respectively [17]. The *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system have also been implicated in opioid analgesia, and blockade of NMDA receptors during TENS prevents the development of analgesia tolerance [29]. It has also been suggested that tolerance is a consequence of an adaptive change by the nervous system to regular repetitive stimuli produced by TENS [32]. This hypothesis led to an incorporation of parameter modulation (such as frequency and amplitude) in most TENS devices; as described before, the usefulness of these modulations still lacks strong scientific evidence. Analgesic tolerance to TENS, however, seems to result from tolerance at opioid receptors in the central nervous system, and uses known opioid-tolerance mechanisms.

The temporal summation protocol used in this study reflects the central excitability from deep tissue pressure pain. It is believed that temporal summation is a consequence of wind-up of dorsal horn neurons [73]. High-frequency TENS decreased temporal summation on day 1 when compared with pre-TENS temporal summation; however, this decrease was not different from placebo TENS. Interestingly, the reduction in temporal summation in both groups was not present on day 5, likely a result of opioid tolerance. Because TENS and placebo effects are opioid mediated [2,5,16,42,68,75], we suggest that repetitive activation of opioid receptors leads to analgesic tolerance by reducing the effectiveness on temporal summation. It is not clear, however, why subjects receiving low-frequency TENS did not show a difference in temporal summation because µ-opioid agonists, the receptor involved in low-frequency TENS analgesia, reduce temporal summation in human subjects [25] and wind-up in animals [21]. It is possible that strong muscle contractions observed in this group could have sensitized the extensor mass of forearm, impairing the TENS-induced hypoalgesic effect.

An important but not surprising finding is that tolerance to TENS did not affect the DNIC response, leading us to conclude that descending systems were not involved in analgesic tolerance. However, it should be pointed out that although both DNIC and TENS use endogenous opioid mechanisms to produce analgesia, they do this through activation of different pathways. Specifically, DNIC activates neurons in the subnucleus reticularis dorsalis in the caudal–dorsal medulla [7,66,67], which are rich in µ-opioid receptors [47,48]. On the other hand, TENS utilizes the periaqueductal gray and rostral ventral medulla to produce an opioid-mediated analgesia [16,34,62].

In summary, the findings presented in this novel study support that both high-and low-frequency TENS produce analgesic tolerance by the fourth and fifth day of treatment, respectively. These data extend and validate prior studies in animals showing tolerance to TENS [9,17,29]. Future studies should be performed to find ways to delay and prevent the occurrence of tolerance to repeated TENS in humans.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Acknowledgements

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