The Analgesic and Antihyperalgesic Effects of Transcranial Electrostimulation with Combined Direct and Alternating Current in Healthy Volunteers

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BACKGROUND: Transcranial electrostimulation (TES) has been reported to produce clinically significant analgesia, but randomized and double-blind studies are lacking. We investigated the analgesic and antihyperalgesic effects of TES in validated human experimental pain models.

METHODS: In 20 healthy male subjects we evaluated the analgesic and antihyperalgesic effects of TES60Hz and TES100Hz to heat and mechanical pain in experimentally induced ultraviolet B skin sunburns and in normal skin. Previous animal studies in our laboratory predicted that TES60Hz would provide significant analgesia, and TES100Hz was a suitable active control. The study was conducted in a double-blind, randomized, 2-way cross-over fashion. TES was administered for 35 minutes. Quantitative sensory testing evaluating heat and mechanical pain thresholds was conducted before TES, during TES, and 45 minutes after TES.

RESULTS: TES (TES60Hz > TES100Hz) evoked rapidly developing, significant thermal and mechanical antihyperalgesic effects in the ultraviolet B lesion, and attenuated thermal pain in unimpaired skin. No long-lasting analgesic and antihyperalgesic effects of a single TES treatment were demonstrated in this study.

CONCLUSIONS: TES produces significant, frequency-dependent antihyperalgesic and analgesic effects in humans. The characteristics of the TES effects indicate a high likelihood of its ability to modulate both peripheral sensitization of nociceptors and central hyperexcitability.
normal and inflamed skin. For the latter, we used a validated experimental model of inflammatory cutaneous pain produced by ultraviolet B (UVB) irradiation (UVB, or sunburn lesion). The UVB lesion is characterized by induction of stable primary hyperalgesia (increased pain sensitivity within the inflamed area)\(^{18–20}\) and reproduces many components of inflammatory response that accompanies acute tissue damage caused by trauma or surgery.\(^{21–25}\) It also demonstrates high sensitivity to analgesic and antihyperalgesic effects of anti-inflammatory drugs\(^{18,24,26}\) and opioids,\(^{23,27,28}\) making it possible to compare the magnitude of TES-induced analgesic effects with those of benchmark pharmacological treatments.

**METHODS**

The study was approved by the Stanford University IRB, and the informed consent was signed by all the subjects. Twenty healthy Caucasian men, ages 20 to 49 years (mean 27.9 ± 9.2 SD), with normal weight and height, were enrolled in the study. The subjects were pain free, had an unremarkable medical history, did not take any prescription or over-the-counter medications, and agreed to abstain from alcohol and nicotine use for the duration of the study. The subjects were required to keep consistent bedtime and wake-up time for at least 3 days before each study day, and to get at least 7 hours of uninterrupted night sleep. The subjects were instructed to keep their normal pattern of food and caffeine consumption and to avoid any strenuous physical exercise on each study day. The subjects with a history of habitual alcohol and tobacco use, drug abuse, history of seizures, documented or suspected organic brain disease, eye disease, head or eye injury, history of surgery on the head or eye, skin lesions of the head, dental implants, and implanted medical devices were excluded from the study. The enrolled subjects did not participate in any other research protocols.

The study was conducted in a randomized, double-blind, 2-way cross-over fashion, with at least a 1-week washout period between the TES study sessions. A computer-generated randomization schedule assigned an equal number of subjects to receive TES\(_{0.01T}^\text{Hz}\) or TES\(_{100T}^\text{Hz}\) on the first study day and the alternative treatment on the second study day. The operator of the TES device, research subjects, research personnel assessing subjects’ analgesic responses to TES, and the personnel collecting and entering the study data were blinded to the TES modality used. Heat pain thresholds (HPTh) and mechanical pain thresholds (MPTH) (see below) were assessed in normal skin and the UVB lesion at a baseline (before TES session), 15 minutes after the start of TES, and 45 minutes after TES was stopped. The subjects were adapted to all experimental procedures before the beginning of the study. Each study session was performed in a quiet room in the morning hours, and light snacks and noncaffeinated drinks were available to the subjects ad lib during the study days.

**Induction of the UVB Lesion**

Before induction of the UVB lesion, the minimal erythemal dose (MED) was determined for each subject, by simultaneously irradiating the subject’s skin with 5 increasing doses (range from 40 to 100 mJ) of UVB light via a calibrated UVB source (Saalmann Multitester SBB LT 400, Saalmann GmbH, Herford, Germany). A small experimental UVB lesion (1.5 cm in diameter), located on the nontanned skin of the upper thigh, was induced with a dose equal to 2 × MED 24 hours before each of the TES study days; the location of the sunburn was rotated between the thighs for different TES sessions. Experimental UVB inflammation is painless during and after induction, does not cause skin damage, is associated with small interindividual variability, and allows for the conducting of repeated and reproducible nociceptive testing.\(^{18,23,26,29}\) The hyperalgesic nature of the UVB lesion was confirmed by a stable decrease in HPTh and MPTH at the site of inflammation before the beginning of each TES session.

**Experimental Procedures**

Using quantitative sensory testing (QST), we assessed the sensitivity to heat and mechanical pain consecutively in both, the UVB lesion and normal skin of the thigh, at sites 20 cm apart.

**Thermal (heat) pain testing.**\(^{24,30}\) A hand-held thermode (16 × 16 mm) connected to a sensory analyzer (TSA 2001, Medoc Advanced Medical Systems, Minneapolis, Minnesota) was brought into full contact with the skin. Starting from the adaptation temperature 35°C, the thermode temperature was increased at a rate of 1°C/s (cutoff 52°C). At the first perception of pain, the subject pushed a button on a hand-held device triggering a computerized recording of HPTh, and an immediate probe-cooling at a rate of 10°/s. This procedure was repeated 7 times with a stimulus interval of 30 seconds, and the average HPTh was computed for data analysis.

**Mechanical pain testing.**\(^{24,30}\) MPTH was determined with the aid of custom-made, calibrated, punctuated pressure probes comprising stainless steel wires (240 μm diameter), mounted on copper rods of various weights (1, 2, 4, 8, 16, 32, 49, 64, and 81 g), and surrounded by a wider hand-held aluminum tube that allowed the wires to move freely inside. Starting with the lightest probe, we applied progressively stronger punctuated stimuli by positioning the steel wire tip perpendicular to the skin surface, so that the weight of the rod rested solely on the wire tip. Once the sensation of pain was elicited, consecutively lighter probes were used to record the transition from pain to no pain. A total of 7 data points were sought: 4 measurements reflecting a change from nonpainful to painful stimulation, and 3 measurements reflecting the opposite change. The average of these 7 data points was computed as a true MPTH, and was entered for data analysis.

**TES procedure.** The custom-made, constant-current TES apparatus includes controls for manual adjustment of pulse duration, DC:AC ratio, TES frequency, and current value, and is in compliance with the safety standards established by the Stanford Hospital Instrumentation and Electrical Safety Committee. The TES current value is continuously displayed on the front panel of the TES device. Subjects were positioned comfortably in a reclining chair. TES was administered through a cathode (10 × 5 cm), positioned on the forehead above the eyebrows, and paired retromastoid anodes (5 × 5 cm), all held in place by Velcro straps comfortably tightened around the subject’s head. Each
electrode consisted of a stainless steel plate and a flannel pad soaked in water, and was brought in direct contact with the subject’s skin. To standardize stimulation intensity for both TES60Hz (active treatment) and TES100Hz (active control), the current was gradually adjusted by the operator to achieve a maximal tolerable, but comfortable (nonpainful) tingling sensation under the electrodes. Once the cutoff current value of 5 mA was reached (DC:AC current ratio was 2:1 [1, 16]), it was maintained at that level for the entire duration of TES procedure. The polarity of stimulation was manually switched by the operator every 10 minutes to prevent a DC charge transfer and to reduce the risk of electrolytic skin burns.31 The total duration of the TES procedure was 35 minutes, upon which current was discontinued and the electrodes removed from the subject’s head.

Statistical analysis. A power analysis indicated that studying 20 subjects would result in approximately 80% chance of obtaining statistical significance via repeated-measures analysis of variance (ANOVA), assuming a large effect size of 0.8.32 Treatment effects were analyzed with a linear mixed-effects modeling approach, using the lme function of S-Plus (version 6.2, Insightful, Seattle, Washington). Mixed-effects models that account for correlation between repeated measures provide a more powerful and flexible tool for analyzing grouped data, in comparison with traditional statistics. Two levels of grouping were used: the factor subject and the factor date, indicating the day on which the experiment was conducted (random effects).33 The contrasts option was used to estimate the effect of the treatment levels (TES60Hz and TES100Hz during and after TES application) on HPTh and MPTH in comparison with the baseline value (fixed effects). \( P < 0.05 \) was considered statistically significant.

**RESULTS**

The maximal current of 5 mA was reached for each study subject during each TES session, typically within the first 5 minutes of stimulation, and was maintained at that level throughout the entire TES procedure. A subjective tingling sensation under the electrodes was identical for both TES60Hz and TES100Hz, assuring appropriate blinding of the subjects. Overall, the subjects tolerated TES procedures well. One subject complained of a transient poststimulation headache, lasting 15 minutes.

Study results are presented in Figure 1 and Table 1. Figure 1 shows the effect of different TES frequencies on HPTh and MPTH in normal skin and in the UVB lesion, during and after
cessation of TES treatment, and Table 1 provides a model estimate of real population values. The development of thermal and mechanical hyperalgesia was confirmed in the UVB lesion, as was evidenced by decreased HPTh and MPTh at the site of inflammation in comparison with noninflamed skin (estimated HPTh decrease 6.8°C, 95% confidence interval [CI] 6.2° to 7.3°C; MPTh decrease 11.6 g, 95% CI 9.5 to 13.6 g). The administration of TES60Hz significantly attenuated heat hyperalgesia in inflamed skin (estimated increase in HPTh: 1.2°C, 95% CI 0.7° to 1.6°C, \( P < 0.0001 \)), and also provided significant analgesic effect to noxious heat in noninflamed skin (estimated increase in HPTh: 0.3°C, 95% CI 0.0° to 0.6°C, \( P = 0.039 \)). In contrast, TES100Hz had no effect on HPTh in normal skin, and was 2.5 times less effective than was TES 60Hz in reducing primary heat hyperalgesia in the UVB lesion (estimated increase in HPTh: 0.5°C, 95% CI 0.0° to 0.9°C, \( P = 0.037 \)). TES60Hz significantly reduced mechanical hyperalgesia in inflamed skin (estimated increase in MPTh: 8.5 g, 95% CI

### Table 1. Model Estimates of the Effects of Different Transcranial Electrostimulation (TES) Frequencies on Heat and Mechanical Pain Thresholds (HPTh and MPTh) in Normal Skin and Ultraviolet B (UVB) Lesion

<table>
<thead>
<tr>
<th>Normal skin mechanical</th>
<th>Fixed effects</th>
<th>Estimate (g)</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td>Versus baseline</td>
<td>Baseline</td>
<td>30.6</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>60D</td>
<td>5.8†</td>
<td>-1.0</td>
</tr>
<tr>
<td></td>
<td>60P</td>
<td>-2.8†</td>
<td>-9.6</td>
</tr>
<tr>
<td></td>
<td>100D</td>
<td>-0.9†</td>
<td>-7.7</td>
</tr>
<tr>
<td></td>
<td>100P</td>
<td>-2.3†</td>
<td>-9.0</td>
</tr>
<tr>
<td>Random effects†</td>
<td>Subject</td>
<td>15.2</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Day</td>
<td>10.9</td>
<td>6.8</td>
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</table>

<table>
<thead>
<tr>
<th>Normal skin heat</th>
<th>Fixed effects</th>
<th>Estimate (°C)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Versus baseline</td>
<td>Baseline</td>
<td>48.7</td>
<td>48.1</td>
</tr>
<tr>
<td></td>
<td>60D</td>
<td>0.3†</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>60P</td>
<td>-0.3†</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td>100D</td>
<td>0.1†</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>100P</td>
<td>-0.4†</td>
<td>-0.7</td>
</tr>
<tr>
<td>Random effects†</td>
<td>Subject</td>
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<td>0.7</td>
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<tr>
<td></td>
<td>Day</td>
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<td>0.4</td>
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<table>
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<tr>
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<th>Fixed effects</th>
<th>Estimate (g)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
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<td>Versus baseline</td>
<td>Baseline</td>
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<td>12.5</td>
</tr>
<tr>
<td></td>
<td>60D</td>
<td>8.5†</td>
<td>3.9</td>
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<tr>
<td></td>
<td>60P</td>
<td>-0.5†</td>
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<tr>
<td></td>
<td>100D</td>
<td>1.5†</td>
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<td>Day</td>
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<th>UVB lesion heat</th>
<th>Fixed effects</th>
<th>Estimate (°C)</th>
<th>95% confidence interval</th>
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<tr>
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<td></td>
<td>60P</td>
<td>0.3†</td>
<td>-0.1</td>
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<tr>
<td></td>
<td>100D</td>
<td>0.5†</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>100P</td>
<td>-0.3†</td>
<td>-0.7</td>
</tr>
<tr>
<td>Random effects†</td>
<td>Subject</td>
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<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Day</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

\( B = \) baseline; 60D and 100D = HPTh and MPTh during TES\(_{60Hz}\) and TES\(_{100Hz}\); 60P and 100P = HPTh and MPTh post-TES\(_{60Hz}\) and post-TES\(_{100Hz}\); SD = standard deviation.

\( * P < 0.05. \)

\( † \) Change from baseline.

\( † † \) It is assumed that random effects have a mean of zero and follow a Gaussian distribution.
are also highly sensitive to opioid compounds in QST, 27,29

DISCUSSION

Our study is the first to demonstrate that TES with DC:AC

mechanical hyperalgesia in the UVB lesion (8.5 g; Table 1).

REFERENCES

1. Nekhendzy V, Fender CP, Davies MF, Lemmens HJ, Kim MS,

Boyle DM, Maze M. The antinociceptive effect of transcranial
electrostimulation with combined direct and alternating cur-

2. Lebedev VP. Transcranial electrostimulation: a new approach
(experimental and clinical testing and equipment). Biomed
Engl 1997;31:66–73

effect of TES60Hz over TES100Hz confirms the results of
our animal study, identifying TES60Hz as the preferred
antinociceptive frequency, 1 and further validates our rat
model of cutaneously administered TES as an accurate
experimental paradigm for future exploration of TES an-
inociceptive effects and mechanisms of action.

In conclusion, we have demonstrated that TES evokes
significant, rapidly developing, frequency-dependent (TES60Hz > TES100Hz) antihyperalgesic and analgesic ef-

fects. Preliminary QST comparison places TES half as
effective as remifentanil (0.05 mcg · kg⁻¹ · min⁻¹), steady-
state concentration 1.3 mg · mL⁻¹) in achieving 50% MAC
reduction of isoflurane. A seeming ability of TES to effec-
tively modulate altered central processing of nociceptive
input, presumably by nonopioidergic mechanism(s), con-
stitutes one of the most conspicuous findings of our study,
suggesting the potential role of TES in clinical pain man-
agement. The future of this technique will rest on the
confirmation studies directly elucidating the mechanism(s)
of TES60Hz action, exploring its effects in experimental
human pain models of secondary hyperalgesia and allo-
dynia, and demonstrating the presence of the analgesic
and antihyperalgesic aftereffects of prolonged or repetitive TES
application.
TES Produces Antihyperalgesic and Analgesic Effects


Ischemic Preconditioning Attenuates Pulmonary Dysfunction After Unilateral Thigh Tourniquet-Induced Ischemia–Reperfusion: Erratum

In the article that appeared on page 539 in the August 2010 issue of volume 111 of Anesthesia & Analgesia, in Table 2 on page 541, one of the footnotes was incorrect:

“T2–4 = 2 hours, 6 hours, and 24 hours after tourniquet deflation” was incorrect.

The correct footnote should be: “T2–5 = 0.5 hours, 2 hours, 6 hours, and 24 hours after tourniquet deflation”

This error has been noted in the online version of the article, which is available at www.anesthesia-analgesia.org.

Reference: