Methods:
A total of 119 patients with chronic pain.

Subjects:
Trial.

Design:
stimulation as a non-invasive method of reducing pain.

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PAIN REDUCTION USING TRANSCRANIAL ELECTROSTIMULATION: A DOUBLE-BLIND “ACTIVE PLACEBO” CONTROLLED TRIAL

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Objective: To examine the efficacy of transcranial electrical stimulation as a non-invasive method of reducing pain.

Design: A randomized, double-blind, placebo-controlled trial.

Subjects: A total of 119 patients with chronic pain.

Methods: Patients were treated with either transcranial electrical stimulation or an active placebo device. Short- and long-term follow-ups were evaluated for treatment efficacy with 4 ordinal scale variables: visual analogue scale (pain level), SLEEP (how often does pain disturb sleep), FREQ (frequency of pain) and MED (frequency of use of medications to relieve pain).

Results: Pain level decreased significantly in the transcranial electrical stimulation-treated group compared with the active-placebo group 3 weeks after the end of treatment ($p=0.0017$ between groups). Other parameters did not demonstrate significant differences. Three months after the end of treatment this effect was maintained and other treatment parameters showed similar improvements.

Conclusion: Transcranial electrical stimulation is an effective non-invasive method for pain relief. The active placebo device has a powerful effect on reported pain, which diminishes in the long-term. The involvement of possible neural mechanisms is discussed.

Key words: electrostimulation, transcranial, active placebo, chronic pain, double-blind.

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INTRODUCTION

People with chronic pain are predisposed to experiencing multiple impairments in their physical, social and psychological well-being. In Israel, the overall prevalence of people with chronic pain is estimated at 17%, of whom 60% are women and half suffer from severe chronic pain. Overall, approximately 40% report that their pain is inadequately controlled, causing a significant impact on employment status (1). The search for therapies that sufficiently and directly relieve pain is ongoing. Since the innovative research performed by the French physiologist S. Leduc in 1902, who, while trying to elicit anaesthesia or sleep, achieved a narcosis-like condition in experimental animals, the use of brain stimulation for analgesia has been studied intensively (2). Percutaneous transcranial electrical stimulation (TCES) is a non-invasive brain stimulation technique that may reduce pain. This alleviation was evident in both human and animal studies, showing an immediate and prolonged effect (3–7). A theoretical explanation for the mechanism of pain reduction by TCES suggests that the electrical stimulation activates the anti-nociceptive system in the brain, resulting in β-endorphin, serotonin and noradrenaline release (8, 9). This hypothesis is supported by studies showing lower levels of β-endorphin in the cerebrospinal fluid (CSF) of patients with chronic pain (10), rapid increase in β-endorphin levels in animal and human blood plasma and CSF during TCES treatment, and increased β-endorphin levels in anti-nociceptive structures in the brain (6, 9, 11, 12). In addition, it was shown that naloxone reversibly suppresses the electroanalgesia in rats (9), and that an effective electrical current stimulation of anti-nociceptive structures in the brain can be detected by imaging device (13). Nevertheless, TCES continues to be a debatable technique with an ambiguously defined mechanism.

In research into electroanalgesia, only a few published experiments used “active TCES placebo”, which, unlike the usual sham placebo devices, gives the patient the feeling of truly being treated. The placebo effect is considered very powerful when treating pain: at least 40% of patients receiving the placebo treatment report pain relief; a finding that is also supported by imaging results (14, 15). The “active TCES placebo” applies a lower amplitude and frequency current with the same options of amplitude adjustment that the patient has with TCES, resulting in a narcosis-like condition in experimental animals, the use of brain stimulation for analgesia has been studied intensively (2). Percutaneous transcranial electrical stimulation (TCES) is a non-invasive brain stimulation technique that may reduce pain. This alleviation was evident in both human and animal studies, showing an immediate and prolonged effect (3–7). A theoretical explanation for the mechanism of pain reduction by TCES suggests that the electrical stimulation activates the anti-nociceptive system in the brain, resulting in β-endorphin, serotonin and noradrenaline release (8, 9). This hypothesis is supported by studies showing lower levels of β-endorphin in the cerebrospinal fluid (CSF) of patients with chronic pain (10), rapid increase in β-endorphin levels in animal and human blood plasma and CSF during TCES treatment, and increased β-endorphin levels in anti-nociceptive structures in the brain (6, 9, 11, 12). In addition, it was shown that naloxone reversibly suppresses the electroanalgesia in rats (9), and that an effective electrical current stimulation of anti-nociceptive structures in the brain can be detected by imaging device (13). Nevertheless, TCES continues to be a debatable technique with an ambiguously defined mechanism.

This study was designed to test whether treatment with TCES reduces pain over a long period of time (i.e. 3 months) in patients with chronic, persistent pain. Additionally, the study sought to disprove the null hypothesis that TCES and placebo treatments are equally effective. The study was designed and executed in accordance with institutional guidelines and the Declaration of Helsinki and was approved by the institutional committee for human subjects’ research.

METHODS

Participants
All participants were patients with chronic pain who were admitted to the pain clinic of the Kaplan Hospital in Rehovot, Israel. The patients...
were screened for inclusion/exclusion criteria (see below) and signed an informed consent after receiving a full explanation of the aim of the trial and the procedures involved. Upon enrolment they were instructed how to assess their pain level by means of a visual analogue scale (VAS), from 0 (no pain) to 10 (maximal pain level). Demographic data, medical history and physical examination were recorded before treatment. Dependent variables were measured at baseline, 3 weeks and 3 months following 8 treatment sessions. The analysed data refers to patients who completed 3 months follow-up.

The inclusion criteria were one of the following conditions: cervical pain, chronic lower back pain (LBP) for more than 3 months (Agency for Health Care Policy and Research criterion of chronic pain, 16), or headaches (migraine, tension and other headaches meeting the diagnostic criteria of the International Headache Society); Man or woman aged 20–70 years; Confirmed diagnosis of intervertebral changes or non-specific back symptoms.

The exclusion criteria were: Orthopaedic or radiologically potentially serious spinal conditions; Involvement in litigation, hydrocephalus, epilepsy, glaucoma, malignant hypertension, pacemaker or other implanted electronic device; Recent cerebral trauma, nervous system infection, skin lesions at sites of electrode placement; Oncological disease; Patients undergoing any other treatments for pain (patients were allowed to continue taking medications in a rescue fashion for the relief of pain, as needed; Any invasive therapy, e.g. surgery, within the last month.

Instruments

Pulse Mazor Instrument’s Transcranial ElectroStimulator (TCES) equipment, Pulsatilla 1000 (Pulse Mazor Instruments, Rehovot, Israel), consists of a micro-controller based stimuli generator with resident read-only memory (ROM) medical software library. It uses a headset, holding 3 electrodes, composed of conductive rubber silicon materials on an adjustable plastic frame. The electrodes were placed on the head, one on each mastoid bone behind each ear, and one on the forehead. The stimuli generator emits pulses on a fixed and controlled frequency. The maximum electrode current as measured on the forehead electrode is 4 mA, adjustable by the patient to the peak self-tolerated level.

Administration of treatment

A paramedic (other than the evaluating doctor) administered 8 30-min treatment sessions, on 8 consecutive weekdays. The instrument was in mode 3, which is asymmetrical, biphasic shape for zero net charge, 77 Hz of frequency, and 3.3 millisecond of pulse width (± 5%), in a dual-channel current manner. This pulse shape prevents charge accumulation in the tissue. Patients receiving placebo were treated with a 50 Hz signal with maximal current of 0.75 mA (as described previously (6)). The active placebo device was indistinguishable from the real TCES device to the patient and the research staff; it was designed to give the patient the feeling of being treated, inducing an individual sensation of skin numbness or muscle contraction, and had the same option of stimuli current regulation by the patient or caregiver.

The treatments followed the manufacturer’s operating instructions. The patient sat in a comfortable chair adjacent to the instrument and, after administration, was instructed by the paramedic to adjust the current level of treatment to the maximum self-tolerated level. Blood pressure, pulse, and respiratory rate were measured before and after each treatment. The treatment parameters, pain levels (pre-treatment and post-treatment VAS), current amplitude, and vital signs were recorded by the paramedic for all 8 treatments.

Safety issues

No adverse events or side-effects resulting from TCES treatment have been reported. Some patients experienced mild redness of the skin under the area of the electrodes. This redness has not disturbed patients and usually disappeared within 10–20 min, although it sometimes lasted several hours.

Outcome variables

Treatment response was measured over 4 ordinal scale variables: VAS (pain level), SLEEP (how often does pain disturb sleep), FREQ (frequency of pain) and MED (frequency of use of anti-analgesic medications).

Measurements

After enrolment, the patients were given a diary in which they recorded their status during the trial; the diary contained documentation of the response variables (VAS, SLEEP, FREQ and MED) in a self-constructed way. Patients recorded the data for 7 consecutive days prior to the beginning of the treatment, in order to establish baseline values. The diary was also used to document data during the follow-up sessions. In addition, VAS values were documented before and after each of the 8 treatment sessions. The cut-off for efficacy on the VAS scale was designed to detect a minimum difference of 1.5 units between active treatment and control, using a standard deviation of 1.5. This calculation was designed to detect significant differences between the groups using an alpha of 0.05 and a power of 0.80.

Blinding

The paramedic administered treatments based on a computer-elicited randomization list. At enrolment, the investigator assigned the next random number in that patient’s category. The investigator did not have access to the randomization list until study completion. The placebo device was indistinguishable from the active device; both devices contained identifying characteristics (label colour and serial numbers) known only to the manufacturer and revealed to the research staff at the completion of the study. The label colours were changed every 2 weeks, and the manufacturer changed the serial numbers every 2 months. The study coordinator knew which instrument to use according to the diagnosis and random number and recorded the serial number of the instrument in the patient file. Both the patient and the paramedic knew the label colour of the instrument assigned, and this instrument was used for all treatments to avoid use of different instruments during consecutive treatments of the same patient. The serial number code was not disclosed until the end of the study.

Statistical analysis

Baseline data for the 2 groups were compared using t-tests (age and pain) and χ² tests (sex ratio). Repeated sessions were analysed using multifactorial repeated measures analysis of variance (SAS Software, Cary, NC, USA). Further comparisons were made using non-parametric tests: differences from baseline within each group were tested using Wilcoxon signed-rank tests, and the comparisons of treatment vs control groups (for all variables) were performed using Wilcoxon 2-sample tests.

RESULTS

A total of 119 patients met the inclusion criteria and were enrolled in this study, all with either cervical, lower back or headache chronic pain (n = 42, 33 and 44, respectively). After obtaining their informed consent, patients were divided into TCES treatment group (n = 58) and active-placebo treatment group (n = 61). The distribution of patients (by cervical pain, LBP and headache, respectively) in each group was 19, 17 and 22 for the TCES treatment group, and 23, 16 and 22 for the active-placebo group. Baseline data were compared as described above, demonstrating no significant differences between the groups in any of the parameters. Demographic data are presented in Table I.
The variables VAS, SLEEP, FREQ and MED were measured at baseline, demonstrating no significant differences between the groups, with the exception of VAS in LBP patients, which were significantly higher for the active-placebo group. A summary of results of the 4 response variables, evaluated by the patients during baseline, are presented in Table II.

Treatment effects
At first follow-up (3 weeks), significant improvements were seen in all measured variables in the TCES treatment group ($p < 0.05$, Wilcoxon signed-rank test). Only patients with LBP did not show any change in the FREQ score, 3 weeks after treatment. In the active-placebo group, a significant improvement was seen in all measured variables 3 weeks after treatment. When divided by type of chronic pain, data showed that patients with cervical pain and headache in VAS scores and LBP patients in SLEEP and MED scores did not show significant changes from baseline (Wilcoxon signed-rank test). At the 3-month follow-up, differences continued to be significant for all comparisons in the TCES group (without the exception of SLEEP and FREQ for the LBP patients), compared with baseline levels. In the active-placebo group, at 3-month follow-up, all response parameters except for MED showed non-significant difference from baseline (Wilcoxon signed-rank test).

Differences between treatment and control groups
When the 2 treatment groups were compared at the 3-week follow-up the difference was significant only on VAS scores ($p = 0.0017$, Wilcoxon 2-sample test). At 3-month follow-up, the treatment group showed significant improvements from baseline in all response variables, compared with the active-placebo group ($p < 0.05$, Wilcoxon 2-sample test). When divided by type of chronic pain both treatments demonstrated no significant effects on all 4 measures of patients with LBP and on MED scores of cervical pain (Wilcoxon 2-sample test). Overall, when divided by type of chronic pain, only patients with headache in VAS scores showed continuous and statistically-significant decreases on both follow-ups, when the 2 treatment groups were compared ($p < 0.05$, Wilcoxon signed-rank test).

When examining the number of patients experiencing pain relief (by means of VAS scores), a larger portion of patients experienced pain relief in the treatment group compared with the active-placebo group (Fig. 1).

### Table I. Demographic data of the 119 patients involved in the study

<table>
<thead>
<tr>
<th></th>
<th>TCES treatment</th>
<th>Headache</th>
<th>Active-placebo treatment</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19</td>
<td>22</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (57.9)</td>
<td>14 (63.6)</td>
<td>13 (56.5)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Age, years, mean (range)</td>
<td>53.9 (36–78)</td>
<td>46.1 (13–78)</td>
<td>52.1 (28–77)</td>
<td>53.6 (27–82)</td>
</tr>
<tr>
<td>Pain duration, years, mean (range)</td>
<td>9.4 (0.5–20)</td>
<td>18.3 (3–40)</td>
<td>1–26 (5.9)</td>
<td>7.8 (0.5–30)</td>
</tr>
</tbody>
</table>

LBP: low back pain; TCES: transcranial electrical stimulation.

### Table II. Patient evaluation of treatment efficacy during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three weeks</th>
<th>Three months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCES Mean (SD)</td>
<td>Active-placebo Mean (SD)</td>
<td>p'</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>p'</td>
</tr>
<tr>
<td>VAS Cervical pain</td>
<td>19 (5.89 (1.66)</td>
<td>23</td>
<td>5.65 (1.64)</td>
</tr>
<tr>
<td>LBP</td>
<td>17 (5.82 (1.81)</td>
<td>16</td>
<td>7.00 (1.51)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (6.20 (2.81)</td>
<td>22</td>
<td>4.59 (3.38)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (5.99 (2.18)</td>
<td>56</td>
<td>6.52 (2.54)</td>
</tr>
<tr>
<td>SLEEP Cervical pain</td>
<td>19 (2.21 (0.92)</td>
<td>23</td>
<td>1.87 (1.10)</td>
</tr>
<tr>
<td>LBP</td>
<td>17 (1.29 (1.21)</td>
<td>16</td>
<td>1.44 (1.36)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (1.55 (1.10)</td>
<td>22</td>
<td>1.45 (1.10)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (1.69 (1.13)</td>
<td>61</td>
<td>1.61 (1.17)</td>
</tr>
<tr>
<td>FREQ Cervical pain</td>
<td>19 (2.58 (0.77)</td>
<td>23</td>
<td>2.74 (0.54)</td>
</tr>
<tr>
<td>LBP</td>
<td>17 (2.59 (0.62)</td>
<td>16</td>
<td>2.81 (0.54)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (1.82 (0.80)</td>
<td>22</td>
<td>1.64 (0.79)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (2.29 (0.82)</td>
<td>61</td>
<td>2.36 (0.84)</td>
</tr>
<tr>
<td>MED Cervical pain</td>
<td>19 (2.53 (1.31)</td>
<td>23</td>
<td>2.48 (1.53)</td>
</tr>
<tr>
<td>LBP</td>
<td>17 (1.82 (1.74)</td>
<td>16</td>
<td>1.94 (1.84)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (3.32 (1.46)</td>
<td>22</td>
<td>3.09 (1.38)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (2.62 (1.60)</td>
<td>61</td>
<td>2.56 (1.61)</td>
</tr>
</tbody>
</table>

*Significance of differences from baseline ($p < 0.05$) within each group (Wilcoxon signed-rank test).

Comparison of TCES vs active-placebo-treatment for differences since baseline (or baseline) data (Wilcoxon 2-sample test).

TCES: transcranial electrical stimulation; VAS: visual analogue score; SLEEP: how often does the pain disturb sleep; FREQ: frequency of pain; MED: frequency of pain medication; LBP: low back pain; SD: standard deviation; NS: not significant.
Influence of TCES on pain reduction

Differences between pre- and post-treatment sessions

Values of VAS were reported before and after each of the initial 8 treatment sessions. An overall repeated measures analysis of variance demonstrated significant improvement for all 3 types of patients. In addition, VAS data improved as the sessions advanced, and the differences between pre- and post-session decreased as the sessions advanced for the headache and patients with LBP. Detailed analysis of the differences showed a significant treatment effect for each session in the treatment group for cervical pain and patients with LBP and for all patients together (Fig. 2). In the active-placebo group, patients with cervical pain and all patients together showed significant session improvements (Fig. 3). Comparison of pre-post session differences of treatment vs active-placebo group revealed that the improvement was independent of the group assignment ($p > 0.05$, Wilcoxon 2-sample test). Comparison of baseline data with the post-session data of the last session showed a similar picture, as no difference was found in improvement between the treatment and the active-placebo group.

DISCUSSION

Over the past few decades it has been observed that direct stimulation of specific neural networks in the brain produces an extremely potent inhibition of pain responses (17). Anatomically, analgesia seems to be concentrated in raphe (medial brainstem, and affected by activation of opiate mechanisms of the anti-nociceptive system of efferent neurons (18). The efficacy of TCES treatment for pain relief is not defined or determined with reference to its proposed mechanism of action. Rather, its efficacy is determined insofar as its ability to reduce pain. Measures of pain, both objective and subjective, provide a quantitative means to evaluate the efficacy of TCES treatments. In the present study we tested the hypothesis that TCES treatment reduces pain over a period of up to 3 months in chronic pain patients beyond an active-placebo treatment. The results, described above, confirm this hypothesis. The results also show that in most patients, significant improvements were established in a 3-week period, for both treatment and sham, proving the significant, although short-lasting, placebo effect. Nonetheless, while the improvement with
TCES treatment remained stable in a 3-month period, the active-placebo effect vanished almost completely in this period, resulting in increased difference in the treatment effect between the groups, and a greater improvement over time for all clinical groups (headache, cervical pain and LBP). At the first follow-up, more than half of the patients of all diagnoses in the TCES-treated group showed a decrease of more than 2 VAS points. This reduction is considered clinically meaningful in terms of morbidity and quality of life (19), and did not vanish at the 3-month follow-up. In contrast, in the active-placebo group, 70–90% of patients from different clinical groups returned to their baseline pain level after the 3-month period.

Both TCES and active-placebo groups showed significant improvement in values of VAS after the first 8 treatment sessions. The active-placebo effect exerted in the area of pain is considered powerful (20); therefore, a comparable initial effect is an expected finding. As reported by a previous study, pain level was reduced in 70–80% of patients from both TCES and active-placebo treated groups. In contrast, β-endorphin blood levels were increased in 70% of TCES-treated patients and in only 20% of patients from the active-placebo group (6). In the present study, the significant active-placebo effect decreased in the longer follow-ups as placebo-treated patients returned to their initial pain level or worsened. Placebo effect and the long-term effect found in the current study indicate complex interactions between neurotransmitter systems (6). Pain relief in the treatment group is demonstrated also by reductions in use of medications and in better sleep patterns. These results are consistent with previous studies showing a positive influence of TCES on insomnia and depressive symptoms (21, 22).

A recent study showed that repeated painful stimulation can result in substantially decreased pain perception, which correlates with decreased blood oxygen level dependent responses in classical pain areas (such as thalamus, insula, secondary somatosensory cortex and the putamen). Interestingly, this habituation effect is accompanied by increased activity of the subgenual anterior cingulate cortex, which is part of the anti-nociceptive system, and therefore may trigger downstream, potentially opioid-dependent mechanisms (25).

Increased activity of the anterior cingulate cortex along with subcortical brain areas involved in opioid-mediated endogenous anti-nociception (such as the amygdala and the pariaqueductual gray) had also been found during placebo analgesia (26, 27). These studies indicate that stimulation itself (either real or placebo), may contribute to the altered pain perception. Nevertheless, the long-term effect of TCES points towards a more complex mechanism, involving inhibitory and excitatory neural pathways (17). To date, the presumed mechanism is related to increased activity of serotonergic and beta-endorphin pathways, which interact in a mutual-dependent fashion (23, 24). Future studies may need to address this issue and request the patients to rate pain intensity of the stimulation itself during the treatment sessions.

**Study limitations**

Given the relatively small number of subjects within each group of patients, treatment efficacy could not be examined reliably on different subtypes of pain. Further studies may be better designed in order to test whether different types of pain correspond differently to TCES treatment. A longer follow-up period (6–12 months) is needed to establish the consolidation of the effect.

In conclusion, although the specific neural mechanisms involved in the action of electrical stimulation on the anti-nociceptive system in the brainstem remain to be studied, the notion of long-lasting effect on pain relief is well-established. The diminished placebo effect over time emphasizes the genuine and reliable long-term outcome of TCES as a method for pain reduction; however, longer follow-up and larger study groups may be warranted.

**ACKNOWLEDGEMENTS**

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5. Capel ID, Dorrell HM, Spencer EP, Davis MW. The amelioration of pain reduction; however, longer follow-up and larger study groups may be warranted.


