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Pain

Research Article

Immediate Influence of Transcranial Electrostimulation on Pain and β-Endorphin Blood Levels
An Active Placebo-Controlled Study

ABSTRACT

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Background: Stimulation of the antinociceptive system by noninvasive electrical current from electrodes placed on the head is a renewed method of pain relief.

Methods: We conducted a randomized, double-blind, placebo-controlled study on 20 chronic back pain patients. They were treated with either transcranial electrostimulation (TCES) or an active placebo device. Pain level and serum β-endorphin levels were measured before and after treatment.

Results: β-Endorphin level increased in seven of the ten patients from the treatment group and did not change in eight of ten patients from control group ($P = 0.057$ between groups). Pain level decreased in eight treated patients and seven control patients (significant decrease for each group, no significant difference between groups).

Conclusions: Transcranial electrostimulation is a nonpharmacologic method of pain relief accompanied or mediated by β-endorphin release. The comparable degree of the initial clinical response emphasizes the powerful placebo effect on reported pain not mediated by endorphin release. This preliminary study shows that noninvasive electrical stimulation is a safe treatment with a positive effect on β-endorphin blood levels.

Key Words: Electrostimulation, Endorphin, Transcranial, Placebo

Percutaneous transcranial electrical stimulation (TCES) is a noninvasive method of brain stimulation that can reduce pain. The idea that there are specific opiate receptors in the brain developed independently but concurrently with the work on electrical analgesia. Chronic pain patients, as compared with controls, have a lower cerebrospinal fluid endorphin level.[1] Treatments of intractable pain by using implanted electrodes, which stimulate specific areas of the brain (caudate, thalamus), are emerging. The proposed mechanisms of deep brain stimulation relate to decreasing pain transmission along sensory-discriminative pathways or to release of endogenous endorphins.[2] Stimulation of periaqueductal gray matter with implanted electrodes in chronic pain patients resulted in significant increases in the concentration of ventricular β-endorphin level.[3]

Pain relief using TCES was evidenced by clinical studies that measured immediate and prolonged pain relief.[4–7] This method has been used in the treatment of chronic pain and in pain in cancer patients.[8] β-Endorphin increase after TCES treatment was found in serum and cerebrospinal fluid of chronic pain patients and controls, but the increment was greater in chronic pain patients.[9] Electroconvulsive shock gives a stimulus 1000 times more powerful than TCES. In addition, it activates endogenous opioid systems that may be part of electroconvulsive shock effects.[10] The existence of antinociceptive systems in the brain and the release of β-endorphins resulting from direct electrical stimulation of these areas are well established.[11] Hence, release of these neurotransmitters was accepted as an explanation of the mechanism of pain reduction by TCES. This hypothesis was supported by the evidence of a rapid increase in β-endorphin concentrations in animal and human blood plasma and cerebrospinal fluid, as determined by radioimmunoassay during TCES, by the evidence of increase in β-endorphin concentrations in the animal antinociceptive structures, and by blocking TCES analgesia by naloxone.[9,12] This was further supported by the results of imaging studies.[13]

There are only a few published experiments in which an "active placebo" was used. The active placebo TCES device, unlike the usual sham placebo devices, was designed to give the patient the feeling of being treated. This feeling is accomplished by applying a lower amplitude and frequency current with the same options of amplitude adjustment that the patient has with TCES. In the area of pain treatments, the placebo effect is considered powerful, even more so when using a subjective measurement method (visual analog scale [VAS]). Improvement can be expected in at least 40% of patients receiving placebo treatment.[14,15]

METHODS

Patients. All patients suffering from chronic back pain or cervical pain who were admitted to our pain clinic during the study period were eligible for this study. The aim of the study and the nature of the treatment were discussed with the patients. The procedures followed were in accordance with institutional guidelines and the Helsinki declaration and were approved by an institutional committee for human subjects research. The patients meeting inclusion/exclusion criteria (see below) gave informed consent after the procedures were fully explained. The patients were taught to assess their pain level by means of the VAS, from 0 (no pain) to 10 (maximal pain level). Inclusion criteria were either sex, ages of 20–70 yr, confirmed diagnosis of intervertebral changes or nonspecific back symptoms (potentially serious spinal conditions were ruled out: orthopedic and radiologic), chronic back pain for more than 3 mo (Agency for Health Care Policy and Research criterion of chronic pain).[16,17] Exclusion criteria were age of <20 and >70 yr, 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, oncologic disease, patients undergoing any other pharmacologic treatments for pain, or any invasive therapy, or surgery within 1 mo before the study. Demographic data, history, and physical examination were recorded before treatment.

Description of Instrument. Pulse Mazor Instrument's Transcranial ElectroStimulator (TCES) equipment, Pulsatilla 1000, consists of a microcontroller-based stimulus generator with resident ROM medical software library. It uses a headset that holds three electrodes, one against the scalp on the forehead and one behind each ear. The stimulus generator delivers strictly controlled electrical pulses independently to the two electrodes on the mastoids at a fixed frequency. The maximum electrode current as measured on the forehead electrode is 4 mA and adjustable by the patient to the peak self-tolerated level. The rigorous, controlled pulses (shape, duration, and frequency) produce a quasi-resonance in the brain and leave no charge accumulation in the tissue.

Administration of Treatment. A paramedical personnel (other than the evaluating doctor) administered eight 30-min treatments on eight consecutive weekdays. The instrument was in mode 3, which is asymmetric, biphasic shape for zero net charge, 77 Hz of frequency, and 3.3 msec of pulse width (±5%). This pulse shape prevents charge accumulation in the tissue. Placebo treatment used a 50-Hz signal with max-

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imal current of 0.75 mA. The active placebo device was indistinguishable to the patient and medical team from the real TCES device—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 stimulus current regulation by the patient or caregiver.

Treatments followed the manufacturer's operating instructions. The patient sat in a comfortable chair adjacent to the instrument and was instructed to adjust the current level of treatment to the maximum tolerated level. Blood pressure, pulse, and respiratory rate were measured before and after each treatment. Endorphin levels were measured before and after the first treatment only. The treatment parameters, pain levels (pretreatment and posttreatment VAS), current amplitude, and vital signs were recorded by the paramedic for all eight treatments. In this study, we report the results of pain and endorphin levels before and after the first treatment. Pain level results and long-term outcome will be reported elsewhere (L. Gabis, unpublished data).

Measurement of VAS Score. The patients reported their score on the VAS before and after each treatment, immediately before the venipuncture. The score was registered on the patient's report form.

Measurement of β-Endorphin Blood Levels. Blood was drawn by venipuncture before and after the first treat-

ment and transferred on ice to the cold centrifuge. All serum samples were stored until the completion of the study. Storage and assay of β-endorphins by iodine-125 radioimmunoassay were according to the manufacturer's protocol (Nichols Institute Diagnostics, San Juan Capistrano, CA). β-Endorphin levels varying by <10% were considered measurement and analysis effects.[18]

Methods of Blinding. The paramedic administered treatments based on a computer-elicited randomization list. At enrollment in the study, the investigator assigned the next random number in that patient's category. The investigator did not have access to the randomization list until after the study was completed. Individuals responsible for the β-endorphin analysis had no exposure to study population.

The instruments differed in label color and serial numbers, known only to the manufacturer. The label colors were changed every 2 wk, and the manufacturer changed the serial numbers every 2 mo. The study administrator 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 color 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.

Outcome Variables. The principal measurement was the β-endorphin blood level. Secondary variables were the pain level reported by each patient (VAS), blood pressure, and pulse. The correlation of these variables was calculated across treatment groups, treatment or control, and for the different current amplitudes.

Statistical Analysis. The data were analyzed using a repeated measures, multifactorial analysis of variance model (SAS software, Cary, NC). The main statistical analysis was a one-way analysis of covariance (treatment *vs.* control), with pretreatment and posttreatment as the main covariable, and other considered covariants were the β-endorphin level and VAS.

RESULTS

Demographic data are presented in Table 1 and results in Table 2. The mean posttreatment β-endorphin level showed an increase of 24.3 pg/ml (SD 37.6) over pretreatment levels in the TCES group and a mean difference of −0.37 pg/ml (SD 6.35) in the control group ($P = 0.03$ between groups). The VAS decreased in both groups—the mean difference between pretreatment and posttreatment VAS was −2.2 (SD 1.7) for the TCES group and −1.2 (SD 1.1) for the control group. The pain level decrease was significant for each group, but there was no significant difference between TCES *vs.* control (*t* test) (Table 2).

The increase in the β-endorphin level in the treatment group was negatively correlated to VAS ($r = 0.5$), a correlation not found in the control group ($R = -0.06$). Eight patients from the treatment group and seven patients from the control group reported a decrease of pain level after treatment. However, an increased β-endorphin level was found in seven patients from the treatment group (range, 111–393%) but in only two

TABLE 2
Pretreatment and posttreatment data

	Treatment		Control		
	Mean	SD	Mean	SD	P
β-Endorphin					
Baseline level, pg/ml	32.8	7.8	32.7	6.7	NS
Level after first treatment, pg/ml	57.1	41.2	32.3	6.1	0.057
P	0.07		NS		
Visual Analog Scale					
Baseline level, pg/ml	6.6	1.4	5.15	2.2	NS
Level after first treatment, pg/ml	4.5	2.7	4	1.8	NS
P	0.003		0.01		

patients from the control group (110%, 141%) .

No significant adverse effects were noticed. All patients tolerated the peak current of 4 mA on the active device and 0.75 mA on the placebo device. Some patients experienced mild redness of the skin under the electrodes. This redness never disturbed patients and disappeared in 10–20 min. About 5% of the patients had mild, short-duration headaches or dizziness during and up to 10 min after treatment. All patients completed the treatment.

DISCUSSION

The observation that electrical stimulation of the mesencephalon in the central gray matter resulted in analgesia began a new era in pain theory.[19] In parallel with studies of TCES and its effects, secretion of morphine-like substances from the antinociceptive area was demonstrated. The present and some previous studies are attempts to establish the connection between these factors. Twenty consecutive chronic pain patients received TCES treatment or placebo. Two endpoints were examined: self-report of reduction in pain and β-endorphin blood levels. The blood was drawn immediately after the first treatment and compared with pretreatment levels. As shown previously, the largest release of β-endorphins occurs after the first treatment, although peak levels may be reached at other times in some patients.[20,21] The pain level was reduced in 70–80% of patients from both treated and placebo groups, as expected from the very powerful placebo effect of an initial appointment with the physician and with the first treatment. In contrast, β-endorphin blood levels were increased in 70% of treated patients and in only 20% of patients from the placebo group. Furthermore, the magnitude of the increase was significantly greater in the treated group. The small change in the control group can be attributed to rest and relaxation.

TCES is a different instrument than transcutaneous electrical nerve stimulation. Conventional transcutaneous electrical nerve stimulation settings are 10–150 Hz for 50–200 μsec. The maximum amplitude of the electrical stimulation produced by the generator was 25 mA using a unipolar square-wave pattern and a pulse width of 0.5 msec, which is a much higher amplitude and a shorter pulse time than the settings of the TCES instrument. Furthermore, the transcutaneous electrical nerve stimulation instrument is placed at the location of the pain (low back, neck), and the TCES instrument is always placed on the head.[22]

In the present study, the influence of the placebo treatment on reported pain level was significant, without a corresponding change in β-endorphin blood levels. Measurement of brain levels of dopamine, serotonin, norepinephrine, and other neurotransmitters indicate that β-endorphins are not the sole neurochemical involved in TCES action.[23] Interactions between neurotransmitter systems reflect further complexities, for example, a mutual dependence of endorphin and serotoninergic systems.[24,7] Moreover, the clinical data presented in this study and a previous clinical study reveal long-term effects of TCES treatment on pain, extending beyond the short duration of action of β-endorphins. Thus, other mechanisms involved in the action of TCES are strongly implicated and remain to be studied.

ACKNOWLEDGMENTS

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