A Collection of
Transcranial Electrical Stimulation
Research Articles, Abstracts, and Reports

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PREFACE:
NEXALIN TRANSCRANIAL ELECTRICAL STIMULATION

The reason for assembling these documents into this collection is to help provide an understanding of the long history of targeted research, clinical studies and product development efforts and how these have collectively been used to evolve the development of the Nexalin Device that is in clinical use today.

The Nexalin technology is based on a patented electrical stimulation that is unique, highly effective and demonstrated safe to the end user. Both in clinical trials and public use, Nexalin Therapy is providing an unprecedented success rate and is dramatically improving the quality of people’s lives while addressing the fundamental symptoms.

We believe it is most important to stress that there are many devices with various purposes and widely different electrical signals as well as electrode types and placements, in the FDA’s category of Stimulators, Cranial Electrotherapy (CES). Other designations include the acronyms TES or TCES. The differences in these devices can be as critical and varied as chemical formulations and dosages in pharmacological products. Even within a single electrical protocol, current level alone can make a significant performance difference. So we caution, as you read through this collection, remember the Nexalin technology is unparalleled by any device available in the market today.

The following pages trace the research and development path from progenitor ideas through the history that assisted and helped direct the early research, and the methods leading to the specific discoveries that are now embodied in the Nexalin Technology.
SECTION 1: THE EVOLUTION AND DEVELOPMENT OF THE NEXALIN TECHNOLOGY
The attempts to obtain analgesic effect by action of electric current upon the brain through the skull were undertaken in France more than 80-years ago. Since that time such attempts have been repeatedly initiated in many countries. In such cases, at the beginning of the research it seemed that the analgesic effect or even electric anesthesia could be easily attained. However, as a rule the results of each individual positive observation were not confirmed during subsequent more thorough experimental testing in a clinic.

The starting aim of the present study resided in experimental determination of the presence and nature of analgesic effect which can be obtained when using transcranial electric stimulation within parameters provided by industrially produced apparatus for electric sleep, electric narcosis and electric anesthesia.

For this purpose the following “electric sleep” apparatus of various modifications were and are being manufactured in our country: “Electronarcon I”, LENAR, portable A-12-01. Basically, the output current characteristics of these devices are similar. They all provide continuous sequence of rectangular pulses of controlled frequency (40-3000-Hz, 0.05-1.0 mA), which can be supplied at the background of an additional constant component (not more than 30% of pulse amplitude). Abroad, the French firm “Thomson-Medicale” manufactures single (unitary) instruments of “Anestelec” [Limog’s device, France] type. This apparatus provides the groups of output bipolar pulses of 3-4-ms duration repeated with the frequency of 77-100 Hz. In this case the frequency of pulses filling the group being 180-kHz with the duration of 1-2-ms.

When choosing the output parameters for devices produced in USSR the experimental researches with the help of quantitative methods practically were not carried out. Besides, the instruments were oriented not to the creation of analgesia but to initiate the state of narcosis or sleep where the quantitative estimation of their manifestation generally presents difficulties and is largely effected subjectively. The experimental grounds for the output parameter of “Anestelec” is also absent in the literature available to us.

The experimental estimation of the analgesic effect manifestation was carried out in tests performed on different species of animals with the help of quantitative procedures usually utilized when determining the analgesic effect of pharmacological agents.

The procedures are based on the measurement of time from the beginning of the pain stimuli till the appearance of motor response of avoidance or measurement of the intensity of autonomic response (e.g. increase of arterial pressure) at standard pain stimuli. The use of quantitative methods enabled to compare with sufficient precision the analgesic effects of actions having various parameters and evaluate the optimal duties.
The experimental check of electric effects within the parameters inherent to the apparatus industrially produced in USSR demonstrated that the primary analgesic effect couldn't be achieved in animals with the use of such actions. As to “Anestelec”, the former initiated a weak increasingly developing analgesic effect in animals.

To find duties for pronounced analgesia, the extensive screening studies of electric parameters were performed. During these studies the frequency and duration of pulses were changed, their replacement with the packs of high-frequency pulses and combination of pulsed and direct currents in various proportion were studied.

As a result, our studies demonstrated that the marked and reproducible primary analgesic effect in animals can be attained when acting upon the brain through the skull with the help of the combination of the fixed frequency and duration rectangular pulses (77-Hz, 3.5-4 ms) or, replacing them, groups of pulses (frequency 10-kHz) and direct current in the proportion of 1:2-1:5. It should be emphasized that the optimal parameters are extremely critical, especially with respect to pulse frequency of packs repetition since with +2-5-Hz deviations the analgesic effect appreciably declines and in order to reach the same level of analgesia the substantially higher currents should be supplied6,7.

In comparable studies in rabbits and rats these parameters induced considerably higher analgesic effect as compared with those of “Anestelec”.

The study of the mechanism of transcranial electric analgesia (TEA) revealed its relation to the excitation of the certain structures of the brain stem and activation of certain neurotransmitter mechanisms. Autographically, with the help of 3H-deoxyglucose, it was demonstrated that transcranial electric stimulation (TES) induced the excitation of antinociceptive neuronal system of some hypothalamus nuclei and periaqueductal gray matter. The analgesia under TES is of opiate character since it has a sensitivity to naloxone, accompanied by the increase of beta-endorphin concentration in liquor [cerebrospinal fluid] and midbrain (radioimmunoassay studies), by competitive displacement of $^{125}$I-morphine in mu-receptors of hypothalamus neurons, periaqueductal gray and raphe nuclei and also by crossed tolerance to morphine. Electro-physiologically, it was found that during TEA the bulbar components of somatosomatic, somatosympatic and viscero-sympatic reflexes were primarily suppressed, thus promoting the stabilization of hemodynamics1,4.

The obtained experimental data enabled to suppose that in man under TES given parameters some effects typical for activation of antinociceptive system could be obtained. At first, in auto-experiments, then during observations on volunteers, the conditions were worked out in order to provide the safety of electric stimulation and eliminate, among other things, the possibility of electric damage of the skin in the area of electrode positioning. In a clinic, the industrially produced apparatus A-30-1, modified specially for providing the necessary parameters, was utilized. In this case, the conditions of patient’s safety were amply observed. The electrodes with thick fabric backings were applied upon the forehead and behind the helices.

The Clinical application enabled to obtain effects as follows.
Analgesia

In a surgical clinic TES was used as an analgesic component of the anesthesia during the most traumatic surgical interventions on heart, lungs, abdominal organs, bones and joints in children and adults with severe attendant pathology being present in most of these patients. The use of TES allowed to completely exclude the administration of opiate analgesics (morphine, promedole, fentanyl, etc.) and markedly decrease the dosages of general anesthetics, used for elimination of consciousness only. After TES application, the marked analgesic after-effect continuing for about 12-hours after the end of operation was noted, with patients being in active state. This enabled to reduce the consumption of opiate analgesics in early postoperative period by more than 75%.

In neuropathological, gastroenterological, cardiological, ophtalmological clinics the marked TES analgesic effect was obtained with various pain syndromes where conventional methods of treatment (drugs, physical therapy) failed to give positive results.

Stabilization of Vegetative Functions

In the process of therapeutic and surgical application of TES it was demonstrated that this effect produced the marked stabilizing action upon the cardiovascular system: stabilization and normalization of arterial pressure is attained, the pressure shifts during pain irritation are eliminated, and the required volume of solutions infused during surgical procedures is reduced. Besides, the marked antivomiting effect is observed manifesting itself with respect to symptomatic nausea and vomiting at cephalgia and pneumoencephalography.

Treatment of Alcohol Withdrawal Syndrome

The withdrawal syndrome in chronic alcoholics, being the endorphin deficient state, was well removed at the TES background without drug therapy. In this case, the elimination or sharp weakening of somatic, vegetative and psychiatric symptoms, typical for alcohol withdrawal, occurred. The questioning of persons subjected to this treatment effected via narcological centers questionnaires, 6-months later after discharge demonstrated more lower return to alcohol consumption.

Wound Healing and Oncostatic Effects

Both effects were revealed and studied only in experiments on animals. It is also scheduled to study in the clinic the combined oncostatic action of TES and of antineoplastic drugs in an effort to potentiate the main effect and decrease the typical side reactions during chemotherapy, mainly vomiting.

In summary, it should be noted that TES, initially developed to obtain the analgesic effect can produce a diversified action upon the organism which in general can be assessed as a distinct homeostatic one.

The future plans involve the refinement of the design of instruments intended for two purposes: for anesthesiology and therapeutic application. It is contemplated to develop a device with several outputs and separate control of each output to provide the
individually dosed effect upon the whole group of patients in one ward, and also instruments for individual application.

Concurrently, the further study of the mechanism of TEA initiation with the aim to find out the rational combination of TEA with pharmacological agents strengthening the analgesic effect. Also, the study of TEA effect upon the elements of the immune homeostasis system shows promise since this is important for understanding the mechanisms of TES wound-healing and oncostatic actions.

References


ANESTHESIA IN LABORATORY ANIMALS
ACHIEVED WITH THE COMBINED EFFECTS OF
DIRECT AND IMPULSE CURRENTS

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Objectives of acute physiological experiments require the exclusion of any pharmacological preparations, which could, in some way, influence the organs under investigation or their operational systems. It is evident, however, that pre-experimental operations require sufficiently deep anesthesia, which could allow to escape the phenomena of pain shock which can profoundly disturb the subsequent functioning of the examined organs and systems. Taking this into account, it is of great importance that the duration of anesthesia should correspond with the operation period and that the anesthetic effect should be completely discontinued before the observation period, i.e., the duration of anesthesia should be deliberately controlled by investigator, and the stimulation, after having been discontinued, should not lead to any consequences.

These requirements seem to be matched by electrostimulation with impulse current which was repeatedly approved experimentally\(^2,4\) and which, at present, has clinical applications. However, certain experimental investigations\(^2,4\) have shown that, in the course of achievement of sufficiently deep anesthesia, almost complications occurred, such as cramps and disturbance of breath and of cardiac function. Additionally, it was noted that the same electric current parameters did not always induce electroanesthesia in subsequent series of stimulation.

The purpose of the present study was to select the parameters of electrostimulation which could induce, in experimental animals, a reproducible electroanesthesia without any of the typical complications. As a starting point, it was taken into account that impulse electrostimulation might be potentiated by a simultaneous supply of direct current via the same electrodes\(^1\).

The main experimental series for selection of electroanesthesia parameters was carried out in rabbits to which electric stimuli were delivered through subcutaneous needle electrodes (cathode was placed at the forehead and two anodic electrodes were inserted behind the ears).

Efficiency of the chosen electroanesthesia parameters was subsequently controlled in the course of experiments in cats and dogs into which subcutaneous lamellar electrodes had been grafted in advance. Narcotic effect was assessed the same way as in rabbits, while analgesia was evaluated according to the change in motor response to mechanical nociceptive stimulation.

For electrostimulation, a commercially available apparatus “Electronarcon-1” was used which allowed to obtain output rectangular or saw-toothed current impulses with the frequency ranging from 50-Hz to 3-kHz and duration time of up to 1-ms, combined with direct current component reaching 20% to the highest possible value of impulse current,
the total current having been not more than 3- mA. In order to expand the possibilities or trial, “Electronarcon-1” apparatus was modified, which allowed to prolongate the duration of impulses as well as to increase the total current value.

In the first experimental series, the effects of rectangular impulses at the frequency range from 50-Hz to 3,000-Hz, 0.1 to 1-ms in duration, with gaps up to 0.5-ms and average current from 0.4-mA to 1-mA, were studied. Frequency was increased in steps of 10-Hz to 100-Hz and of 250 -Hz to 3-kHz. Duration steps were 0.1-ms and current steps were 0.05-mA. In the course of experiment, the complications which had been reported by other authors occurred in rabbits, i.e., arterial hypertension, tachycardia, tachypnea, and cramps which often caused animal death. At the same time, no electroanesthesia could be observed.

In the second series, delivering of similar impulses was preceded by direct current supply via the same electrodes. Direct current was delivered in 0.5-mA steps to reach 2- mA. First signs of anesthesia were observed, in some cases, when direct current component of 1 mA was combined with impulse current 80-Hz in frequency, with 1-ms duration and average current of 0.4-mA to 0.55- mA. With the increase of direct current value to 2-mA and the employment of impulses of the same frequency and duration with average value of 0.8-mA to 1.0-mA, electroanesthesia developed in 68% of cases, in 20% of which cramps occurred 10 to 12-minutes after the development of electroanesthesia. In the remaining 32% of cases there was no electroanesthesia, and the primary effect was represented by cramps. At the same time, isolated action of direct current with similar characteristics did not result in any perceivable response, with the exception of alert reaction at the moment of switching-on. This could be avoided by gradually increasing direct current supply to the required level within 2 to 3- minutes. This series findings have clearly demonstrated that complications occurred, however, in many cases, electroanesthesia could be achieved with the combined effects of direct and impulse currents at the ratio of 2:1, impulse frequency of 80-Hz, and impulse duration time of 1-ms. These current and duration characteristics were the highest ones which could be obtained with the industrially produced “Electronarcon-1” apparatus.

Having taken this into account, in the third experimental series, the possibility was studied to raise the efficiency of electrostimulation by means of the increase of the total current value with the maintenance of the same direct current/average impulse current ratio, and the prolongation of impulse duration. It appeared, as a result of this experimental series, that, with direct current component of 4-mA to 6-mA and impulse current 80-Hz in frequency and 3-ms to 5-ms in impulse duration, electroanesthesia developed without any complications virtually in all cases. In some cases, it was possible to lower impulse current value to the level of 0.2 of the direct current component value.

Final current density measured 3 to 5-mA/cm2. Complete disappearance of motor pain response to nociceptive skin stimulation and suppression of arterial blood pressure response to nerve stimulation were characteristic of electroanesthesia condition in rabbits. At the same time, spontaneous breath was maintained, the rhythm of which slowed down, while arterial blood pressure remained unchanged. After the switching-out
of electrostimulation, no anesthetic after-effect could be observed in rabbits, and their motor activity and pain responsiveness were immediately restored.

The anesthetic effect could be reproduced in the course of repeated electrostimulations. Similar results were obtained in cats and dogs with the same current parameters. Repeated severe pain stimulations of animals during electroanesthesia did not result in any defense reflexes, which suggested the development of a kind of amnesia.

Thus, the combined application of direct and impulse currents allowed to achieve a stable and reproducible condition of electroanesthesia in laboratory animals (rabbits, cats, and dogs), which was characterized by the presence of spontaneous breath and the stability of arterial blood pressure. In contrast to the previously reported methods, in the method of electroanesthesia described in this paper, direct current values were 2 to 5-times higher than those of impulse current, whereas, previously, they had not exceeded 20% of impulse current values. It should be also underlined that duration characteristics of impulse current are critical enough because, when they exceed the limits described above, a sufficient increase in average impulse current value is required in order to achieve the same effect.

Similar results could be obtained if the rectangular impulses were substituted for by the group of high-frequency impulses of the same duration at a frequency of 10-kHz and duration of single rectangular impulse in the group about 50-ms.

In conclusion, it should be noted that gradual increase in the current amplitude described in the third experimental series did not result in gradual development of analgesia and subsequent development of anesthesia. These two conditions both developed simultaneously and not gradually. It could be also noted that, in these experiments, analgesia in rabbits was not reduced after naloxone injection (0.5-mg/kg).

References
CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA

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Abstract

Results of the experiments in rabbits have shown that, under the influence of transcranial electrostimulation with combined direct and impulse currents (77-Hz, 3.5-ms) under conditions of the analgesic effect suppressed by naloxone (0.15-mg/kg body weight), there was a significant increase in beta-endorphin levels in cerebrospinal fluid (CSF; 320%), the midbrain (250%), and dorsal part of the spinal cord (330%) and a slight decrease in its level in the pituitary (82%), whereas the beta-endorphin level in the hypothalamus changed only insignificantly. In normal humans, similar stimulation also resulted in significant increase in the CSF beta-endorphin level (350%). Still higher elevation of beta-endorphin concentration was observed in patients with marked pain syndrome (580%), in which transcranial electrostimulation caused pain relief. It is concluded that, in the development of analgesia with transcranial electrostimulation, an essential role belongs to the activation of endorphinergic mechanisms of the antinociceptive system in the brain stem and the spinal cord.

Key Words: Transcranial Electroanalgesia; Antinociceptive System; Beta-Endorphin.

Since the beginning of this century, there had been numerous attempts to induce analgesia or anesthesia by means of transcranial electrostimulation of the brain\textsuperscript{10}. This method is, no doubt, very attractive; however, it is still not readily available for routine practical application. This could be explained by the fact that electrical parameters which were used for the stimulation up to date, were not enough supported by experimental basis. Therefore, there was a poor reproducibility with this method or, occasionally, its application was associated with cramps.

Recently, the employment of such electrical parameters was proposed that allowed to obtain reproducible analgesic effect in man and to reduce, to a certain extent, the doses of analgesics, neuroleptic, and narcotizing agents usually required for effective anesthesia in surgery\textsuperscript{12}. Our previous observations based on a large-scale experimental screening of electrical parameters\textsuperscript{3} suggested that the most pronounced analgesic effect could be achieved in rabbits with transcranial electrostimulation with the combination of direct current and rectangular impulses at a frequency of 77-Hz and an impulse duration of 3.5-ms, the ratio direct current/average impulse current (DC/AIC) having been 2:1 to 5:1. The use of such stimulation regimens in man (12 mA total current) allowed to achieve profound analgesia which could be employed successfully as a main component of surgical anesthesia without addition of any analgesics and neuroleptics in the course of more than 300-major operations as well as for relieving of pain syndromes (5 mA to 6 mA total current) of various ethiology in more than 350-patients.
Positive clinical findings suggest the need for investigation into the mechanisms underlying transcranial electroanalgesia in order to further improve this method.

Physiological and neurochemical data which have been reported since the beginning of the 1970’s provide an evidence that, in the brain stem, there exists a system of structures the stimulation of which leads to an antinociceptive [medical science concerned with the causes and origins of diseases. ng of pain transmission, usually relating to a receptive neuron for painful sensations] effect in animals and in man. Certain structures involved in this antinociceptive system are rich in opiate receptors and endorphins. An important role is usually ascribed to these structures in the formation of suppressive effects on the conduction of pain impulses at various levels of the central nervous system, beginning with the spinal cord, as well as in the realization of the analgesic effect produced by morphine and other analgesics (for review, see 6,8,11).

It seems probable 4 that the analgesic effect of transcranial electrostimulation might be due to the activation of certain structures in the antinociceptive system. Evidently, in order to elucidate this question, a variety of methods should be employed which could allow to determine specific sites of action in the brain. The aim of this work was to determine, in animal experiments as well as in observations in normal humans and in pain-suffering patients, whether transcranial electrostimulation were associated with the activation of endorphinergic mechanisms, which could suggest that transcranial electrostimulation activated the antinociceptive system. For this purpose, in rabbits and in man, changes of the beta-endorphin level were measured in cerebrospinal fluid (CSF) during and after electroanalgesia as well as changes in the beta-endorphin levels in certain parts of the brain, the spinal cord, and in the pituitary of rabbits.

**Methods**

In our experiments 8-alert Chinchilla rabbits (adult males; isophenotypic [iso = identical, phenotype – Total characteristics displayed by an organism under a particular set of environmental factors, regardless of the actual genotype of the organism]; body weight of 2.85-kg) were utilized.

Transcranial electroanalgesia was performed as previously described5. Total current value reached 7 mA (frequency 77-Hz; impulse duration 3.5-ms; ratio 2:1), the exposition time having been 30-minutes. Current was delivered through thick needles inserted subcutaneously [under the skin] at the frontal side of the head (cathode) or behind the ears (double anode).

Efficiency of electroanalgesia was measured by the alteration of tolerance to nociceptive [process of pain transmission, usually relating to a receptive neuron for painful sensations] stimulation of the hind legs with the use of impulse summation method1. CSF specimens were obtained from the cisterna magna [part of the brain] through a catheter before and 15 and 30-minutes after the beginning of electroanalgesia, and 15-minutes after the stimulation had been ceased. In order to facilitate the suboccipital puncture [under, or posterior to, the occiput; as, the suboccipital, or first cervical, nerve], muscle tissue had been punctured in advance up to
the atlanto-occipital [Anatomical term] membrane with the use of an ultrasound needle of USS-201 apparatus under local anesthesia with 0.25-% Novocain solution.

300-ml CSF specimens were collected with a micro-syringe into tephlene-tubes, each containing 100-ml of 0.86% NaCl solution supplemented with 4.0 x 10^-3 M EDTA, 4.0/10^-3 phenylmethylsulfonyl fluoride (peptidyl peptidase inhibitor; Sigma, USA), and 4% glycerol; pH 7.5. Specimens were mixed thoroughly but without any foaming and then frozen at −70°C. Cell matter was removed by 20-min sedimentation at 760-g in a refrigerator centrifuge K-70.

15-minutes after the end of electroanalgnesia, animals were decapitated. The brain, the pituitary, and L3 and L4 segments of the spinal cord were immediately extracted and placed into 0.86-% NaCl solution at 4°C. The hypothalamus was then separated, from chiasma [part of the brain] to mamillary [a pair of nuclei & associated gray matter in the interpeduncular space rostral to the posterior perforated substance in the posterior hypothalamus] bodies; as well as a median portion of the midbrain at the level of the inferior thalami which contain the central gray matter, and dorsal portions of the spinal cord’s segments above the central canal including the dorsal horns together with the gelatinous substance. To facilitate the penetration, the skull bones and the vertebral arches [anatomical term] were transected with an ultrasound knife of the USS-201 apparatus. Brain tissue dissection was carried out with an ultrasound knife of the same apparatus. The brain portions and the pituitary were blotted with filter paper, placed into tephlene-tubes containing 1 ml of 0.1 N CH₃ COOH at 98°C, and incubated for 15-min., which was a slight modification of the extraction method16.

The brain tissue was disintegrated by ultrasonification [ultrasound] at 4°C for 45-s. Intact cells and cell debris were removed by 20-mm sedimentation at 20,000-g in a refrigerator centrifuge K-24. In order to remove nucleoproteinic [structures containing both nucleic acid and protein] complexes and to improve the selectivity of subsequent procedures, streptomycine sulfate was added to the homogenate at a final concentration of 0.5%. For further measurements, the supernatant was used.

**Clinical Investigation Involved Two Groups of Subject:**

4-normal individuals and 5-patients with marked chronic spondylogenous [Spondylitis - Inflammation of the vertebrae] pain syndrome (age ranging from 31 to 50-years). Examination of CSF was indicated for diagnostic purposes; in the first group, it was required for exclusion from the dermatology-venereal dispensary registration list; in the second group, it was indicated for further elucidation of the nature of pathological process.

Transcranial electrostimulation was performed with the use of supracutaneous [under the skin] metal electrodes provided with thick pads consisting of 16-layers of white flannel moistened with tap water. Cathode was placed at the supraorbital [above the eyes] region of the forehead while parts of double anode were placed against the mastoid processes. Direct current of 3 mA to 4 mA and mean impulse current (77-Hz; 3.5-ms) of 1.5 mA to 2 mA were used. 1-ml CSF specimens were drawn from normal subjects after a standard lumbal [anatomy term] puncture under local anesthesia with
O.5% novocaine three times; before, immediately after 30-mm electroanalgesia session, and 15-mm after its end. CSF specimens from patients were obtained in duplicate, before and immediately after electroanalgesia. Human CSF was then treated the same way as rabbit CSF.

Beta-endorphin concentrations were measured using commercially available beta-endorphin radioimmunoassay kit (Immuno Nuclear Corporation, USA). Assay procedure, including preceding affinity [analytical chemistry technique used to separate and purify a biological molecule from a mixture] chromatography of specimens under investigation with immobilized anti-beta -endorphin antibody linked with covalent bonds to sepharose [Tradename for a gel of agarose] matrix granules was carried out according to recommendations of the above-mentioned Corporation (Catalogue no. 42-12, Part XP0337, 1983) as well as to recommendations given by other investigators. 

$^{125}$I activity of the precipitated tracer was counted using 1280 ULTPOGAMMA gamma counter (LKB, Sweden) in a combination with 1222 DATABOX computer (LKB, Sweden) provided with micro-program support for statistical methods used for production of calibration curve and for calculation of concentrations.

**Results**

Transcranial electrostimulation with chosen parameters caused an average 6-fold increase in the number of impulses, which led to escape reaction in rabbits, suggesting the essential growth of tolerance to noxious stimulation. Analgesic effect, as indicated in the figure 1,A, developed gradually, having reached the maximal value after 10-mm stimulation. Later on, this effect did not change. The same time interval was required after the switching-out of electrostimulation for this effect to disappear.

In a control animal, in the absence of transcranial electrostimulation, the given experimental conditions did not cause any alterations in tolerance to pain (Fig. 1C, 2). Intravenous injection of naloxone at 0.15-mg/kg completely suppressed the analgesic effect, having reduced pain tolerance to the base-line level (Fig. 1B, 2). Control intravenous injection of the same volume of 0.86% NaCl solution had no influence on pain tolerance (Fig. 1A, 1).

CSF specimens were drawn from rabbits at time intervals shown in the figure 1, 1. After 15-mm transcranial electrostimulation, beta-endorphin concentration increased 3.2-times ($p \ll 0.01$), in average, and did not change after the stimulation had been discontinued.

Beta-endorphin concentration values after 15-min and 30-min electroanalgesia did not significantly differ ($p \gg 0.05$), this suggesting that the relationship of beta-endorphin CSF contents to the duration of stimulation throughout this period was of saturation character (Table I). 15-minutes after the end of electrostimulation, beta-endorphin concentration in rabbit CSF decreased significantly ($p <0.05$), with an average of 24% to the previously reached level (Fig. 1A, 1; Table I).

There was a significant correlation between changes in pain tolerance and beta-endorphin concentration in the course of transcranial electroanalgesia in rabbits.
(correlation quotient r = +0.85), suggesting the possible existence of a functional association between these two parameters.

Intravenous injection of naloxone did not influence beta-endorphin concentration in rabbit as CSF during transcranial electroanalgesia (Fig. 1B, 1; Table I). The difference between beta-endorphin concentrations after injections of naloxone and of equal volume of 0.86% NaCl solution was not statistically significant (p >0.05).

Table II and figure 2 show the results of beta-endorphin contents determination in the pituitary and in different portions of the brain obtained from rabbits which were decapitated 15-minutes after the end of electroanalgesia. Significant increase was observed in the median portion of the midbrain (more than 2.5-times) and in the dorsal part of L3 and L4 segments of the spinal cord (average increase 3.3-times). However, in the hypothalamus no significant change could be demonstrated. In the pituitary, a significant average 12% decrease in beta-endorphin concentration was observed (p <0.05).

Transcranial electrostimulation also caused a marked analgesic effect in human subjects. Preliminary study carried out in a group of 20-healthy volunteers had demonstrated, judging by volunteers’ self-assessment, that, approximately after 10-min of stimulation, a slight decrease in pain responsiveness to mechanical irritations and a marked increase in pain adaptation reserve occurred. Furthermore, an analgesic after-effect could be registered.

In patients suffering spondylogenerous pain, complete pain relief or significant reduction of pain level were observed, which occurred after 10 to 15-minutes of stimulation. This was confirmed not only by patients’ self-assessments but also by objective findings, e.g., by the changes in tension symptoms and antalgic [alleviating pain] position. Analgesic after-effect was maintained over a period of 4 to 10-hr, and it could be further prolonged after subsequent sessions. It should be noted that in specific patients examined in this work the electroanalgesic effect was expressed at full, whereas the traditional methods, including physiotherapy and acupuncture, which had been used before, proved ineffective.

Data summarized in table III represent the results of beta-endorphin concentration determination in CSF of normal individuals and in patients with chronic pain syndrome, both before and after transcranial electroanalgesia.

Average beta-endorphin concentration in CSF of normal individuals was 19.1±0.9-pmole/l. Transcranial electroanalgesia caused average beta-endorphin concentration to grow 3.5 times higher (p <0.001) and to reach the level of 67.6±7.6-pmole/l. 15-minutes after the end of electrostimulation no significant changes in the increased beta-endorphin levels could be observed (p <0.05).

In patients with chronic pain beta-endorphin concentration was 1.5-times lower than that in normal subjects and had average value of 11.9±0.8-pmole/l. After 30-min electrostimulation, average CSF beta-endorphin concentration became 5.8-times higher to reach the level of 69.9±7.5-pmole/l (p <0.001).
Statistical analysis could not reveal any correlation between baseline and final concentration values (correlation quotient $r = 0.16$ for normal individuals and $r = 0.23$ for patients with chronic pain). Baseline beta-endorphin concentration values varied to a greater extent in patients with chronic pain than in normal subjects. However, the ranges of final concentration values were virtually similar in both groups.

**Discussion**

Our findings provide an evidence that, under transcranial electrostimulation, there is a sharp increase in beta-endorphin levels in certain parts of the rabbit brain which are associated with the antinociceptive system, and an increase in concentration of this opioid peptide in cerebrospinal fluid, in rabbits as well as in normal human subjects and in patients with pain syndrome.

The fact that the elevation of beta-endorphin concentration accompanies the development of analgesia suggests a possible cause-and-effect relationship between these two phenomena.

Such suggestion seems to be highly probable because of the fact that, as it has been shown in animal experiments, the developing electroanalgesia could be completely suppressed after injection of relatively low doses of naloxone, an opiate receptor blocker. Thus, the two important indirect evidences for the involvement of beta-endorphinergic mechanisms in the brain stem and the spinal cord in the development of transcranial analgesia have been obtained.

In the recent report, Kuzin et al.2* have come to the same conclusion concerning the role of the endorphin mechanisms in electroanalgesia formation. These authors have found in 10-patients pretreated for heart surgery, after stimulation with Limoge current, an increase in CSF beta-endorphin contents comparable to that described in the present work. Additionally, they have demonstrated that blood beta-endorphin concentration also increased, which corresponds with our findings according to which concentration of this peptide in the pituitary lowered.

It is characteristic that the increase in CSF beta-endorphin concentration was demonstrated under the influence of certain factors which led to the development of analgesia, i.e., different types of reflex therapy, cold and immobilization stresses, and un-escaped pain stimulation of extremities; such analgesia having been suppressed, to a lesser or greater extent, by naloxone$. This suggests that transcranial electrostimulation could, to a certain degree, trigger such a mechanism, directly influencing the antinociceptive structures of the brain. Generally, direct stimulation of these structures in animals and in human subjects could be performed through intracranial electrodes, however, application for this purpose of transcranial stimulation with experimentally confirmed regimen provides evident advantages because of its simplicity and safety.

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2* This data was published after the results of this paper had been obtained.
CSF beta-endorphin concentration values which were obtained by us in normal individuals with the use of radioimmunoassay [system for testing antigen antibody reactions] were within the range of values reported by other authors\textsuperscript{19}, as follows: 12.0-pmole/l\textsuperscript{5}; 22.3±1.1-pmole/l\textsuperscript{14}; and 27±7.1-pmole/l\textsuperscript{15}. Higher values of 43.4±8.3-pmole/l had also been reported\textsuperscript{7}. These data taken into account, initial CSF beta-endorphin concentration value of 4.8-pg/ml, or 1.39±0.43-pmole/l, described by Kuzin et al.\textsuperscript{12} appear to be essentially underestimated. This could be due to the fact that, in the latter work, CSF was obtained from patients with severe chronic heart disease.

It should not be excluded also that this discrepancy was caused by technical differences since these authors did not use, for beta-endorphin determination, the highly selective procedure of affinity chromatography with immobilized anti-beta-endorphin antibody, which is, according to Rossier et al.\textsuperscript{16}, an optimal method for isolation and concentrating of this neuropeptide. It is thus probable that CSF specimens were not sufficiently free of matter, which could cause nonspecific tracer immobilization.

Additionally, it could be stated that quite expedient preliminary removal of polypeptide hormone, which was used by these authors, could lead to a partial loss of certain amount of beta-endorphin due to nonspecific sorption, a possible percentage of which was not reported\textsuperscript{2}.

Our findings (Table III) lead to a conclusion that CSF beta-endorphin contents in patients with chronic pain was approximately 63% to that in normal individuals. This result confirms previously reported data\textsuperscript{17} concerning a certain decrease in endogenous opiate contents in CSF of patients with severe chronic pain However, it should be stated that final beta-endorphin levels achieved in normal individuals and in patients with chronic pain were virtually similar (Table III). This fact could provide a slightly modified interpretation for the opinion of Terenius\textsuperscript{17} who postulated that, in chronic pain, the endorphinergic [neurons activated by, characteristic of, or secreting endorphin or substances with similar activity] mechanisms of the antinociceptive system were suppressed due to constant overexertion. Our findings rather suggest that the endorphinergic mechanisms either adapt themselves to chronic pain stimuli or are even checked by these stimuli. In this case, such unusual stimulation as transcranial electroanalgesia could completely trigger the endorphinergic mechanism.

At present, it is not yet clear which specific elements of the brain provide the primary substrate for transcranial electrostimulation. It is hardly likely that such stimulation primarily activates only the brain-stem neurons, which contain endorphins and, as it is known, are small and have short axons. Undoubtedly, in the course of transcranial electroanalgesia, the bulbo-spinal [neuro-physiology term] neurons with long axons are also excited. This seems to provide the only possible explanation for the fact that, during electrostimulation of the brain, the activation of the endorphinergic mechanisms in dorsal horns of the spinal cord occurs.

Additionally, some other data obtained 'at the laboratory of Circulation Physiology, Pavlov Institute of Physiology of the USSR Academy of Sciences, which suggest a more expanded influence of transcranial electroanalgesia on the brain stem than that exerted by narcotic analgesics, could be mentioned. For example, according to A. V.
Krasyukov’s observations, analgesic doses of morphine have only slight influence on pain arterial blood pressure reflexes in rabbits, whereas electroanalgesia leads to a complete suppression of these reflexes. Since these reflexes are restored after naloxone injection during electroanalgesia, it is probable that their suppression also involves the opiate mechanisms, however, with the exception of the elements bearing mu-opiate receptors, which are sensitive to morphine. It could be also mentioned that, according to A. B. Ssvchenko, transcranial electroanalgesia induced in rats by similar stimulation and measured by the suppression of pain response to the stimulation of the hind legs could not be arrested after injection of 0.1-mg/kg to 0.2-mg/kg of naloxone.

Thus, the findings of the present study as well as the results of separate observations which will be published in more detail later demonstrate that under transcranial electroanalgesia the endorphinergic mechanisms of the antinociceptive system of the brain stem and the spinal cord are activated, but this is not the only effect of electrostimulation. Further and more detailed investigations are required into the mechanisms of induction of transcranial electroanalgesia, which could not only be important for practical purposes but could also provide possible ways for elucidation of the pain mechanisms and of the role of the antinociceptive system.

Table I. Change in the beta-endorphin level (pmole/l) in rabbit cerebrospinal fluid (CSF) during and after transcranial electroanalgesia.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>Baseline</th>
<th>15-min</th>
<th>30-min</th>
<th>45-min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.0</td>
<td>7.4</td>
<td>7.1</td>
<td>7.3</td>
</tr>
<tr>
<td>O.86-% NaCl injection</td>
<td>6.9±0.1</td>
<td>23.5±0.5</td>
<td>24.0±0.3</td>
<td>17.9±0.7</td>
</tr>
<tr>
<td>Electroanalgesia</td>
<td>7.1±0.2</td>
<td>23.74±1.0</td>
<td>23.4±0.7</td>
<td>18.0±0.5</td>
</tr>
</tbody>
</table>

* CSF was obtained before and in the middle of electroanalgesia session, immediately and 15-minutes after its end

Table II. Change in the beta-endorphin levels (ng/mg) in the brain tissues and in the pituitary of rabbits after electroanalgesia.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>Pituitary</th>
<th>Hypothalamus- Midbrain</th>
<th>Spinal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>171</td>
<td>348</td>
<td>107</td>
</tr>
<tr>
<td>Electroanalgesia</td>
<td>150±3</td>
<td>351±15</td>
<td>269±11</td>
</tr>
</tbody>
</table>
Table III. Change in the beta-endorphin levels (pmole/l) in cerebrospinal fluid of normal individuals and of patients with chronic pain after transcranial electroanalgesia.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subject no.</th>
<th>Sex</th>
<th>Baseline values</th>
<th>After electroanalgesia immediately</th>
<th>15-min late</th>
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<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>f</td>
<td>19.04</td>
<td>79.96</td>
<td>74.60</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>f</td>
<td>21.30</td>
<td>78.75</td>
<td>67.64</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>m</td>
<td>16.93</td>
<td>64.05</td>
<td>58.73</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>m</td>
<td>18.82</td>
<td>47.51</td>
<td>42.36</td>
</tr>
<tr>
<td>Pool</td>
<td></td>
<td></td>
<td>19.22</td>
<td>68.64</td>
<td>61.05</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>19.0±0.9</td>
<td>67.6±7.6</td>
<td>60±6.9</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>1</td>
<td>m</td>
<td>11.83</td>
<td>59.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>f</td>
<td>12.60</td>
<td>82.78</td>
<td></td>
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<tr>
<td></td>
<td>3</td>
<td>f</td>
<td>15.02</td>
<td>86.82</td>
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<tr>
<td></td>
<td>4</td>
<td>m</td>
<td>9.56</td>
<td>73.99</td>
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</tr>
<tr>
<td></td>
<td>5</td>
<td>m</td>
<td>10.77</td>
<td>46.31</td>
<td></td>
</tr>
<tr>
<td>Pool</td>
<td></td>
<td></td>
<td>12.14</td>
<td>70.65</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>11.9±0.9</td>
<td>69.9±7.5</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1 ON THE NEXT PAGE
Fig. 1. Change in tolerance to pain and in beta-endorphin concentration in rabbit cerebrospinal fluid in the course of transcranial electrostimulation (A and B) and in control (C).
1 - endorphin concentration.
2 - tolerance to pain.

Ordinates: in the left, number of impulses causing escape reaction; in the right, beta-endorphin concentration, pmole/l.

Abscissae: time, min. Transcranial electrostimulation period is marked by horizontal bar above the abscissae. Arrows in A and B mark the moments at which 1-ml of 0.86% NaCl and 1-ml of naloxone (0.15-mg/kg) were injected intravenously.
Fig. 2. Change in the beta-endorphin levels in different structures of the rabbit brain after transcranial electrostimulation.
Schematic presentation\(^{13}\) of frontal sections of the rabbit is given as follows: (1) the hypothalamus at the infundibulum [anatomy term] level; (2) the midbrain at the posterior thalami level; (3) the pituitary; and (4) the spinal cord at the level of L4 segment.
The portions examined are marked with the interrupted line Sections are shown at different scales. The heights of the columns reflect, in relative units, the beta-endorphin levels in control (in the left) and after transcranial electroanalgesia (in the right), according to table II.
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TRANSCRANIAL ELECTROANALGESIA IN THE TREATMENT OF SPONDYLOGENOUS PAIN SYNDROMES

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SUMMARY

The analgesic effect secondary to transcutaneous brain stimulation with direct and impulse currents (rectangular impulses; frequency of 77-Hz; impulse duration of 3.5-ms) at a ratio of 2 to 5:1 was studied. This effect was observed in both healthy subjects and in patients with spondylogenous pain. The analgesic effect lasted for six to ten hours following a 30-min therapeutic session. A 5 to 7-session course resulted in gradual increase and stabilization of the analgesic effect. No complications occurred during and after the procedure.

Arresting of spondylogenous pain syndromes represents an important problem in practical neurology. At present, the use of traditional methods usually does not provide sufficiently rapid and pronounced analgesic effects. For this reason, the attempts to develop new methods as well as to evaluate their effectiveness for the treatment of spondylogenous pain have not yet been ceased. Acupuncture (1, 2) and transcutaneous electrostimulation (2) should be mentioned in this connection.

Our objective was to investigate the possibilities for application of a new electroanalgesia method which previously had been approved in the course of animal experiments (4) and had been positively evaluated in the course of clinical trial in the treatment of postoperative pain (3).

The essence of this method consists of the combined stimulation of the skull with direct current and rectangular impulses. According to our experimental findings (3, 4), the current parameters, which could cause an analgesic effect, are rather critical ones. In our opinion, the analgesic effect is based on the stimulation with rectangular impulses (75 to 80-Hz in frequency; impulse duration of 3 to 4-ms). The role of direct current consists of that, when used at ratios of 2:1 to 5:1 to the average impulse current value, it will block cramp effects, which occur in laboratory animals with the isolated application of impulse current. In addition, under the influence of direct current, there is a significant decrease in cutaneous tissue impedance, which allows to enhance the impulse current value without any increase in voltage and, thereby, to improve the latter’s analgesic effect.

The effects of transcranial electroanalgesia (TEA) were studied in 25-young healthy volunteers and in 91-patients with spondylogenous pain syndromes. TEA was performed with the use of a modified Electronarcon-1 apparatus. This modification provided the prolongation of rectangular impulse duration up to 4-ms and the increase in the output current values up to 15 m A cathode was placed on the frontal surface and two anodic electrodes were pressed against the mastoid processes. In order to avoid
skin burns, which might have been caused by electrostimulation, 16-layer-thick white-flannel pads moistened with warm water were used.

At first, direct current was delivered, and its value was slowly increased to reach 3 to 4 mA level within one to two minutes. Subsequently, impulse current stimulation was switched on which led to pressure, vibration, and stitching sensations in patients. Impulse current value was similarly slowly increased within one to two minutes to reach the highest tolerable level of about 1 to 1.5 mA. During the stimulation, which lasted for 30 to 40-minutes, the above sensations were reduced, which allowed to increase the current value, some patients being tolerant to as great a total current value as that of 10 mA. Appearance of burning sensation under the frontal electrode indicated the likelihood of burn development if the stimulation with direct current of such amplitude would have been continued. In these cases, the direct current value was reduced until the complete disappearance of such sensation. With healthy volunteers, current parameters were maintained at constant levels throughout the procedure, that is, 3.5 mA for direct current and 1 mA for impulse current.

The analgesic effect exerted by TEA upon our patients was judged by observing changes in their pain responsiveness, which was evaluated with the use of A. A. Rudzit's algometer (5) while pricking the patients' skin on the inner surface of the arm with pressure measured in grams. Pain threshold value and adaptation “reserve” were estimated. The latter meant the difference between needle pressure threshold value which could cause rapidly transient pain sensation and pressure value which did not lead to any adaptation to pain sensation within ten seconds. In healthy subjects, these parameters were initially determined in advance within 2-hr and subsequently measured during TEA session and after its discontinuation. During these measurements, arterial blood pressure (ABP) and cardiac and respiratory rates were determined.

Figure 1, which represents our findings with healthy volunteers indicates that, during TEA session, a certain gradual increase in pain-responsiveness threshold value occurred, this increase being the most significant one after 20-min stimulation. More marked changes could be observed in adaptation “reserve”. Also in this case was the maximal effect observed after 20-min of stimulation. As shown in the figure 1, after the discontinuation of TEA session, any of these parameters did not immediately return to the baseline value, which provides an evidence for the existence of analgesic after-effect. During the procedure, there were no significant and regular changes in ABP and cardiac and respiratory rates. Similarly, no changes either in muscle tone or in tension reflexes could be observed. Volunteers' communicative and orientational abilities remained unchanged during as well as after the procedure. Two of the volunteers felt somnolence during the stimulation. Thus, in healthy volunteers, a certain decrease in pain responsiveness could be demonstrated during and after the procedure.

Basing upon these findings, we administered TEA to 91-patients with spondylogenous pain. Among these patients, 56-were males and 45-were females. Patients’ mean age was 42-years. In 53-cases pain syndrome was caused by osteochondrosis in the lumbar region (group I), whereas in 38-cases it was caused by osteochondrosis in the cervical region of the spine (group II). In the group I, disease lasted in average for 2 to
3-years, its duration being, in some cases, as long as 20-years. Current exacerbations lasted from one-day to eight-months.

In all group I patients radicular pain syndrome had been diagnosed; mostly associated with reflex lumbo-ischialgic syndrome and muscle tone disturbances of diverse markedness. In eight of 53-patients in whom disc sequester prolapse into the neural canal had been diagnosed (x-ray contrasting; subsequently verified in three-patients during the surgery), stable and severe static and dynamic disturbances were found in the spine.

In the group II, disease lasted in average for 2 to 5-years, current exacerbation period ranging between one-day and three-months. This group included patients with different kinds of pain syndrome, i.e., radicular syndrome in 2-cases and reflex syndrome in 17-cases (in 7-patients it was associated with cervico-cranialgia and in 10-patients it was associated with cervico-brachialgia and cervico-pectalgia with muscle-tone and autonomic vascular manifestations).

Markedness of pain syndrome was assessed in complex, i.e., judging by patients’ self-estimation, markedness of tension symptoms, and presence of antalgic position. For the subjective pain assessment, a five-point scale was used (extremely severe pain—4-points; severe pain—3-points; pain of medium intensity—2-points; slight pain—one-point; and the absence of pain—zero). Tension symptoms were assessed by angles at which patients’ leg could be lifted (Lasegue’s symptom) and patients’ arm could be drawn aside. In the group I, in eight-patients with disc sequestration, following pain intensity levels were registered according to subjective pain assessment: 4-point pain was observed in two-patients, 3-point pain in two-patients, 2-point pain in three-patients, and one-point pain in one-patient. The leg-lifting angles in these patients were 15° in three patients, 45° in four patients, and over 45° in one-patient. In 45 group I patients without disc sequestration, 4-point pain level occurred in 8-cases, 3-point pain level was registered in 24-cases, 2-point pain level was found in 4-cases, and one-point pain level was found in 2-patients. Leg-lifting angles were 15° in 10-cases, up to 45° in 26-cases, and over 45° in 9-cases.

Among 38-group II patients, 4-point pain level occurred in 8-cases, 3-point pain level was registered in 24-cases, 2-point pain level was found in 4-cases, and one-point pain level was observed in 2-patients. The arm side-lifting angles were determined in 30-patients. They measured up to 45° in 14-cases and up to 90° in 16-cases.

TEA procedure was considered effective if pain was reduced not less than by two-points or disappeared completely and if leg or arm-lifting angles increased by 20° or tension symptoms completely disappeared, all these effects persisting for not less than 4-hr. In all of the remaining cases, the procedure was considered to be ineffective. The treatment course was regarded to be effective if leg or arm-lifting angles increased by more than 40°, this effect persisting for more than two-weeks following the last procedure. Statistical significance of this effectiveness was evaluated with the use of White’s nonparametric criterion test.
TEA effectiveness evaluation results are represented in the table I. Effective TEA procedure usually produced pain reduction after 15 to 20-minutes of treatment, this reduction becoming more pronounced by the end of the procedure. The procedure appeared to be the most effective in group II patients and in those group I patients who had no disc sequestration.

The effect was absent in two patients with low pain level (one-point) and long-lasting pain syndrome (5 to 6-months) who had been undergoing outpatient as well as inpatient treatment for a long time. In contrast, the highest degree of effectiveness was found under condition of high pain level (3 to 4-points). It should be also noted that the procedure appeared to be the most effective when performed within the first week of exacerbation period. No distinct relationship between the procedure effectiveness and the duration of exacerbation period within a range from one week to six months could be found.

During the treatment course, the analgesic effect increased with each subsequent procedure, the duration of analgesic after-effect being gradually prolonged. This finding is represented in the figure 2 which demonstrates the dynamics of treatment course effectiveness according to changes in leg-lifting angle in group I patients without disc sequestration. These mean data include the results obtained while examining those patients in whom at least a single procedure in the treatment course could be considered effective. As it is shown in the figure, the analgesic effect generally increased during the treatment course, although, if judging merely by formal criteria, the last few procedures could be regarded as low-effective ones in certain patients (minor changes in pain intensity under condition of its low initial level or minor increase in leg-lifting angle under condition of its great initial value). After the discontinuation of the treatment course, a stable analgesic after-effect persisted.

TEA treatment appeared to be low effective in 8-group I patients with disc sequestration.

In our experience, TEA did not induce any side effects. During TEA, certain sedative effect and improvement of sleep were observed in our patients, which might be, to a certain extent, associated with pain reduction. In several cases, a decrease in ABP could be registered in patients with arterial hypertension after repeated TEA procedures, which might be also due to pain relief. In three of 91-patients, at the end of the procedure and after its discontinuation, slight and transient dizziness was observed.

It should be noted that TEA was effective also in those patients who had been previously treated with non-narcotic analgesics, physiotherapy, and acupuncture without any significant success. TEA maybe readily used in a combination with physical exercises since, due to TEA treatment, the patients become less restricted in their motor activities and these activities are rendered less painful. TEA advantages include the possibility to achieve an effect immediately during the procedure or soon after its discontinuation as well as the high reproducibility, technical simplicity, and availability of this method for paramedical personnel.
References

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Table I. TEA effectiveness in the treatment of spondylogenous pain syndromes

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Single procedure</th>
<th>Course of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>I (n=53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (n=45)</td>
<td>36*</td>
<td>3</td>
</tr>
<tr>
<td>B (n=8)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>II (n=38)</td>
<td>31*</td>
<td>7</td>
</tr>
</tbody>
</table>

Degrees of effectiveness are as follows:

I highly effective;
II moderately effective; and
III ineffective.
A without disc prolapse;
B with disc prolapse.
*p <0.01
ARRESTING OF PAIN SYNDROME AND AUTONOMIC RESPONSES DURING PNEUMOENCEPHALOGRAPHY WITH THE USE OF TRANSCRANIAL ELECTROANALGESIA

V. A. Sorokoumov, S. I. Gretsov, R. I. Voytenko, A. A. Skoromets, V. P. Lebedev, Ya. S. Katsnelson, And G. S. Kokin

Air or oxygen introduction into the submeningeal space, pneumoencephalography (PEG) and pneumomyelography (PMG), is still frequently employed in neuropathology and neurosurgery for diagnostic and therapeutic purposes. These procedures are generally known to induce severe headache in the majority of patients; marked autonomic responses, i.e., vomiting and the development of a condition which is close to collapse, may be also observed. Headache usually persists for several days and is enhanced dramatically with each change in patient’s position, which makes patient to restrain his physical activities. Administration of narcotic analgesics cannot liberate patients from such painful sensations during PEG, and, not infrequently, this drug therapy has to be repeated on subsequent days.

Stimulation of meningeal receptors during PEG is mainly achieved via the trigeminal nerve system, which is a particularly active reflexogenic zone. Several authors reported successful treatment of prosopalgia and cephalgia by means of transcutaneous electrostimulation (A. Borromei et al., 1982; H. Schmid a. M. Angelberger, 1983), corporal and auricular acupuncture, and electrosleep (N. M. Shcherbakov et al., 1969). There are no data available concerning the application of these methods for analgesia during PEG and PMG. Therefore, we made an attempt to employ a new method of transcranial electroanalgesia (TEA) for this purpose. The main point of this method consists of the combined stimulation of the skull with rectangular electric impulses at frequencies of 75 to 80-Hz and an impulse duration of 3 to 4 mA which produce the analgesic effect and with a direct current component 2 to 5-times as great in its amplitude as the average impulse current component (V. P. Lebedev et al., 1983). TEA was performed with the use of a modified “Electronarcon-1” apparatus. Standard electrodes of this apparatus, that is, a cathode applied at the forehead and a double anode placed against the mastoid processes, were employed. The electrodes were provided with 16-layer thick flannel pads moistened with warm water in order to prevent skin burns, which might have been caused by direct current effect. During the procedure, while patients were becoming accustomed to the sensations of pressure, vibration, and slight stitches, the current amplitude was gradually increased. Appearing of burning sensation under the frontal electrode indicated the possible development of burn and required to reduce direct current until this sensation would have disappeared.
TEA treatment was undertaken during PEG procedure which was performed for diagnostic and therapeutic purposes in 12-patients (three-female and nine-male patients; patients age ranged from 15 to 46-years) with cerebral arachnoiditis as well as 1 to 3-days after PMG procedure administered in six-male patients (aged 18 to 27-years) in association with traumatic injuries of the spinal cord roots.

Twenty minutes before the PEG onset, patients were given intra-muscular injections of 0.5-ml 0.1% atropin solution and 2.0-ml 0.5% seduxen solution (narcotic analgesics were not used), after which the TEA session was immediately begun. This treatment was continued also during the introduction of air over a period of 15 to 25-minutes. Air was introduced slowly in small portions after the removal of the cerebrospinal fluid. The final introduced air volume ranged from 50 to 110-cm$^3$ with an average of 75-cm$^3$. During the PEG procedure, considerably greater current values could be usually achieved (average impulse current value of 3.0 to 5.0 mA; total current value of 6 to 13 mA) as compared with those achievable during the treatment for other pain syndromes. It has been demonstrated that, under TEA, the patients fixed their attention mainly on the sensations of pressure and slight stitches under the frontal electrode and did not suffer any increase in their headache with the introduction of each subsequent portion of air. After the discontinuation of the TEA session, the patients relatively little complained of their headache, having qualified it as moderate one in 10-cases and as medium one in 2 cases in spite of the continuing air introduction.

A vomiting episode occurred in one-patient and nausea was observed in six-patients. Combined application of PEG and TEA was not associated with any clinical manifestations of epileptic activity in 11-patients. In one-female patient with recent history of Jackson's cramps in her right arm, similar isolated episode 1 to 2-minutes in duration occurred under conditions of air introduction and TEA.

During subsequent 3 to 5-hr after PEG, headache brought only minor troubles to the patients; however, in the evening, it increased to such an extent that injections of usual doses of non-narcotic analgesics were required, after which all patients could sleep at night.

There is an impression that the subsequent dynamics of PEG-induced pain syndrome also changed under the influence of TEA session. Thus, there were no complaints of headache on the following day, and no vomiting episodes occurred due to the changes-in patients' position so that the patients who still kept their bed regime maintained their motor activities. The patients could relatively soon lift some regime restrictions; four of them started to walk in the evening after PEG, four patients began to walk on the following day, and the remaining four-patients could walk on the third day after PEG.

In six-cases, TEA was performed secondary to complaints of severe headache, pain along the spine, nausea, and vomiting at the end of the one to three-day period after PMG during which approximately 60-cm$^3$ of air had been introduced endolumbally; all these patients were compelled to keep their bed regime.
Headache was characterized by the patients as being very severe and hardly tolerable in four-cases, severe in one-case, and of medium intensity also in one-case. In all patients, the 30-min TEA session resulted in complete headache relief. It is noteworthy that, shortly before TEA, three patients complained of severe nausea which could be significantly reduced as early as 7 to 10-minutes after the beginning of the session i.e., before the patients could notice that their headache was decreasing; subsequently, nausea disappeared completely. Discontinuation of nausea and headache was accompanied with marked somnolence [sleepiness] in four cases; all patients slept well all night long without administration of any analgesics or somnifacients and could walk on the following morning. Only in one-patient did intensive headache and nausea return 4-hr after the procedure due to an abrupt turning of his head; repeated TEA session was effective once again.

Thus, hypoalgesia achieved with the use of the method under investigation is sufficiently pronounced and prolonged in order to successfully reduce pain syndrome secondary to PEG and PMG and provides the shortening of the whole period of headache duration as well as the shortening of bed-regime period following these procedures. According to our preliminary data, transcranial electroanalgesia performed one to three-days after PMG can also arrest autonomic responses caused by the penetration of air into the submeningeal space and the brain ventricles.

Summary

A new method of transcranial electroanalgesia was employed during and after pneumoencephalography and pneumomyelography. It has been demonstrated for the first time that the achieved analgesic effect allowed a significant reduction of pain syndrome developing during and after the air introduction into the submeningeal space and the brain ventricles.

References


Despite the more than a century of research into ulcerative disease, the problems of pathogenesis and treatment of this disorder are still of great medical and social importance. The urgency of these problems is due to the fact that a method of treatment which could affect all the mechanisms of pathogenesis in order to normalize regeneration, secretion, and motor functions of the gastrointestinal tract has had not yet been found.

Recently, it has been discovered that administration of opioid peptides and their synthetic analogues exerted reparative and cytoprotection effects on the gastrointestinal tract organs\(^{(3,4,9,10)}\), which led to application of these agents to the gastroenterology practice. Additionally, it has been demonstrated that direct stimulation of antinociceptive zones in the brain containing opioid structures resulted in the acceleration of reparative processes\(^{(5)}\). The present study was aimed at the examination of the effects of transcranial electrostimulation (TES) at a regimen that provided brain opioid mechanism activation\(^{(2,6,7,8)}\) on the healing processes in gastric and duodenal ulcers.

TES method was employed for the treatment of 272-patients with ulcerative disease during the endoscope confirmed exacerbation of this disorder. Patients’ age ranged from 18 to 74-years. 89 of them suffered from ulcerative disease of the stomach (UDS) which was primarily diagnosed during our investigation in 14-patients. 183-individuals had ulcerative disease of the duodenum (UDD), in 48 of whom it was diagnosed for the first time during our study.

Complex therapy for ulcerative disease included injection of high molecular-weight proteins (aminokrovin, 500.0-ml intravenously, drop by drop, 5 to 7-transfusions) and nucleotide-derived reparants (1% to 5% ethadene, intramuscularly, 10-injections per treatment course) and, if necessary, symptomatic treatment, i.e., administration of antacids (almagel or vicalin), spasmolytics [antispasmodic], tranquilizers, and other drugs. According to study protocol, patients were divided into two groups. One of these two groups included those patients for the treatment of whom, together with traditional therapy, TES was used (TES group). Patients of control group were treated with traditional methods alone. TES was performed with the use of a modified “Electronarcon-1” apparatus at a regimen designed according to our previous experimental findings\(^{(1)}\).
The method consisted of transcranial stimulation with a combination of direct and impulse currents (rectangular impulses; frequency of 77 to 78-Hz; impulse duration of 3.5 ms), direct current/average impulse current ratio being 2 to 5:1. Electrodes were applied frontally and retromastoidally, with hydrophilic pads. Mean total current value measured 5 to 7 mA. Two protocols for TES were designed as follows:

1) Daily treatment at 20 to 30-min exposure, treatment course including 7 to 10-sessions;

2) Treatment two times a day at 20- to 30-min exposure, treatment course including up to 20 sessions.

**Observation protocol included:**

1) General clinical examination; determination of biochemical blood serum parameters of protein, lipid, and carbohydrate metabolism; examination of the autonomic nervous system’s condition;

2) Endoscope examination that provided the diagnosis of ulcerative lesion’s condition. Treatment surveillance was carried out at the intervals of 10 to 12-days. Ulcerative lesion reparation rate was expressed as mm²/day (ulcerative lesion area) in mm² divided by the number of days which formed an interval between the two endoscopic examinations: the initial one, when ulcer had been diagnosed, and the second one, when ulcerative lesion’s epithelization [regeneration of epithelium] could be demonstrated;

3) In several patients of the experimental group blood plasma levels of beta-endorphin (BE) and gastrin (G) were evaluated by means of radioimmunoassay in the course of treatment;

4) Acid-producing function of the stomach was examined with the use of the fraction probing method (examination was carried out with the utilization of histamine stimuli, i.e., submaximal histaminic test) and pH measuring;

5) Psychological diagnostic methods included examination of the personal relation type using the personality questionnaire designed at the V. M. Bekhterev Scientific Research Institute of Psychiatry (Leningrad).

In all patients, the treatment resulted in the achieving of clinical remission in their disorder: pain syndrome and dyspepsia episodes could be arrested; the patients began to feel better, their sleep became normalized, and they gained in their body weight. However, in the experimental group clinical remission occurred somewhat earlier as compared with the control group the patients of which were treated with traditional methods.

Thus, we could observe stable disappearance of tachycardia, normalization in arterial blood pressure, appearance of sedative effect, and headache relief in the majority of
patients as early as after 3 to 4-TES sessions, which was not the case with the patients of control group at the comparable time intervals.

Questioning of the patients with the use of range-scale test before the therapy and immediately after TES treatment revealed a significant decrease in pain intensity, which could be confirmed by a decrease in pain range index and number of selected descriptors in the course of questioning employing the method of poly-dimension semantic pain description.

After each TES session, analgesic after-effect could be observed within a period of 4 to 15-hours while analgesic effect appeared 15 to 20-minutes after the beginning of stimulation.

Examination of laboratory parameters demonstrated insignificant decrease in hypercholesterolaemia, elevation of blood albumin contents, and reduction of elevated gamma globulin levels.

Endoscopic control of ulcerative lesion epithelization revealed an essential acceleration of healing processes. Thus, whereas with traditional treatment healing rates in UDS and UDD were respectively 1.17±0.23 and 1.76±0.58 mm²/day, with daily single TES sessions these rates increased respectively to 3.05±0.28 and 2.39±0.3 mm²/day, and with daily TES two times a day they were 4.15±0.28 and 3.07±0.37 mm²/day. Such treatment allows essential shortening of inpatient period for patients with ulcerative disease.

Blood plasma beta-endorphin (BE) levels in UDS and UDD patients did not differ from those in normal individuals (9.11±1.03 and 9.2±0.4-pmole/l respectively). TES treatment caused significantly less pronounced elevation of BE levels in UDS and UDD patients than it did in healthy subjects and in patients with pain syndrome (21.05±3.02, 31.86±4.72, and 31.18±5.21-pmole/l respectively). In UDS and UDD patients, the treatment led to a stable elevation in blood BE levels to 16.9±2.77-pmole/l. The fact that the brain opioid structures’ response was reduced in UDS and UDD patients during early TES sessions requires further investigation.

Gastrin (G) contents in UDS and UDD patients ranged between 29.9+ and 126.4-ng/l. As a whole, G levels tended to decrease in our patients (from 81.03±16.58 to 66.85±11.2-ng/l). In order to examine the possible relationship between plasma G and BE concentration changes (table 1), the patients were divided into three groups according to their initial G contents: those with low (up to 50-ng/l), medium (50 to 90-ng/l), and high (more than 90-ng/l), which showed a strong direct correlation to BE level changes (r = +0.93). In contrast, there was a tendency towards G level reduction in the group with initial G contents (in average, from 103.63±14.03 to 83.26±14.51-ng/l) with a reverse correlation between the two parameters under examination (r = -0.67).

Data thus obtained indicate that, under the influence of TES, certain gastrointestinal tract neurohumoral regulation mechanisms are normalized. The question whether this is of pathogenic importance for ulcerative disease patients remains to be answered.
Psychological diagnostic testing of patients on the day of hospitalization and, subsequently, after endoscopically confirmed remission revealed a strong predominance of neurasthenic alarmabell, and hypochondriac individuals among the patients. Ulcerative lesion healing rate was significantly greater in most neurasthenic patients as compared with other subjects. Epithelization rates in these patients were 37% (UDS) or 18% (UDD) greater than in other patients of control group. The type of personal relations did not change under the influence of TES.

Thus, our findings allow us to estimate positively the TES method and provide an evidence for the possibility of its application as a simple pathogenic therapy method with high reparative effect in ulcerative disease, which could be used for inpatient as well as for outpatient treatment. This method could be recommended for an increasingly wide application for ulcerative disease management.

Table 1. Relationship between blood plasma gastrin and beta-endorphin levels in patients with ulcerative disease of the stomach and the duodenum treated with TES.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Gastrin, ng/l</th>
<th>Beta-endorphin, pmole/l</th>
<th>Correlation quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td>before treatment</td>
<td>after TES</td>
<td>after TES</td>
<td>before TES</td>
</tr>
<tr>
<td>Low initial gastrin level</td>
<td>36.45+</td>
<td>50.55+</td>
<td>50.72+</td>
</tr>
<tr>
<td>Remaining patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>88.87+</td>
<td>70.2+</td>
<td>74.01+</td>
</tr>
<tr>
<td></td>
<td>19.78</td>
<td>14.67</td>
<td>18.01</td>
</tr>
<tr>
<td>high initial gastrin level</td>
<td>103.62+</td>
<td>79.36+</td>
<td>83.26+</td>
</tr>
<tr>
<td></td>
<td>14.03</td>
<td>12.87</td>
<td>14.51</td>
</tr>
</tbody>
</table>
Abstract

In 272-patients with ulcerative disease of the stomach and the duodenum (experimental group) and 80-patients of control group, the influence of transcranial electrostimulation (TES) on the clinical course of disease, ulcerative lesion healing rate, and blood plasma gastrin and beta-endorphin contents was studied. It has been demonstrated that ulcerative disease treatment supplementation with TES accelerated the achieving of clinical remission and reparative processes and led to a decrease in gastrin and to an increase in beta-endorphin blood plasma contents.
METABOLISM OF BIOGENIC AMINES DURING THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME BY TRANSCRANIAL ELECTRIC TREATMENT

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Clinical, physiological and biochemical studies indicate that transcranial electrical treatment (TET) [a.k.a. TES], comprising a combination of constant current with pulse current of square impulses of 70-80-Hz frequency is efficient in stopping alcohol withdrawal syndrome (AWS). The parameters in the impulse component are of crucial importance: a 10-Hz change in the impulse component frequency abolishes the medical effect. The beneficial effect of TET is due to the activation of the brain endorphinergic systems; this activation seems to bring back to normal the metabolism of biogenic monoamines, which were disturbed in the development of AWS.

Key words: alcohol withdrawal syndrome; transcranial electric treatment; biogenic amines metabolism; beta-endorphin.

Introduction

In the state of alcohol withdrawal syndrome (AWS) considerable metabolic alterations occur in the organism, in particular the metabolism of neurotransmitters is damaged (Sytynskij, 1980). The alterations in. the metabolism of catecholamines seems to be most important in the pathogenesis of AWS (Hawlay et al., 1981; Anokchina and Kogan, 1984; Eisenhofer et al., 1985).

Thus, a direct proportionality was found between the elevation of blood dopamine level and the expression of AWS signs (Kogan, 1981; Anokchina, 1984). In most studies disturbances of serotonin metabolism were also found (Oksenkrug et al., 1977; Bullenger et al., 1979). One of the possible causes of the disturbances of biogenic amines metabolism in AWS are the changes of activity of its enzymes: blood plasma and platelets monoamine oxidases, dopamine-beta-hydroxylase, etc. (Agarwal et al., 1983; Anokchina and Drosdov, 1984). The degree of these alterations reflects the severity of withdrawal symptoms. Thus, the results of clinical and biochemical studies of AWS may serve for the evaluation of its severity, and therefore for that of the effect of its therapy.
Gisak (1983). Blood platelets were isolated by the routine method (Baluda et al., 1980) after which their type B monoamine oxidase activity (MAO-B) was determined with benzylamine as substrate (Voloshina and Mosquitina, 1986). Radioimmunoassay method was used for the determination of the plasma beta-endorphin level as it was described by Ayrapetov et al., (1985).

In the course of the treatment the patients of the major and the 2nd-comparison groups underwent an additional test: their omega-potential, which is known as the steady-potential in mV-range, was determined. Both its background value and that after a single physical exercise (10-squatting) were determined. The omega-potential was discretely taken in the lead from the head surface (in the vertex region) in relation to the hand thenars [palm of hand or sole of foot] (Iliukchina, 1986).

In order to shed light on the effect of TET modifications on the dynamics of the blood plasma beta-endorphin level during and after its application, 5-healthy volunteers and 5-patients with chronic pain syndrome (lumbosacral radiculitis) were given TET in the form of a combination of constant current and square impulses of frequency 70-80-Hz (1st-series) and 90-100-Hz (2nd-series) followed by a radioimmunoassay of the plasma beta-endorphin level before, during and after TET.

**Results**

Table 1 represents the comparison of different methods of AWS treatment, their efficiency being assessed according to the integrate data of AWS expression, the latter including the sum of average values of all examined symptoms. It is evident that AWS was most efficiently halted in the major group, i.e. under the action of constant current no less than 3-4 mA, combined with pulse current with square impulses 70-80-Hz frequency and 3.5-4 ms duration. Intramuscular Relanium injections also halted AWS, the effect, however, being less than that of TET in the conditions mentioned (the difference in the state of patients in the first two-days is significant). TET applied in other combinations in the groups of comparison exhibited poor results in AWS medication: no statistically significant therapeutic effect could be observed (Table 1).

It is significant to mention that TET in the form of a combination of constant current with pulse current of 70-80-Hz frequency, resulted in AWS stopping in 2 or 3-days. As early as 1-2-hours after the first TET application the expression of most of the symptoms was reduced by 50% and over. TET in the major group at the 4th and 5th-days was aimed at abolishing the asthenic postabstinental state and the residual AWS symptoms.

**Biogenic amines and beta-endorphin metabolism during stopping with TET**

Only one form of TET was effective in stopping AWS, namely that of a combination of constant current with pulse current, square impulses with 70-80-Hz frequency. That is why our studies of the catecholamine and indolamine metabolism, and the blood beta-endorphin content during AWS treatment were performed in this TET condition. The results are presented in Table 2.
As is seen in Table 2, blood dopamine content significantly decreased on the 4th-5th-day. The dopamine level tended to already decrease 1-2-hours after the first TET application, which is in agreement with the onset at this time of a considerable clinical improvement in the patients of the major group. The blood serotonin omega-potential, contributing to its onset in the interval of 30-40 mV, and causes its significant increase by 4-8 mV on the 5th, 6th and 7th-min after physical exercise, in relation to the respective values of the omega-potential before TET.

It should be emphasized that in the group of comparison in which the AWS was stopped with TET in the form of a combination of constant current and pulses of 90-100-Hz frequency after TET application, neither significant changes in the background values of omega-potential nor in its dynamics in response to physical exercise were observed.

Discussion

The results of the present research prove beyond any doubt that TET in proposed conditions (combination of constant current with pulse current of 70-80-Hz frequency) efficiently stopped different symptoms of AWS. The conditions of treatment are of crucial importance: a 10-Hz shift in frequency resulted in a considerable decrease in medical effect. It should be emphasized that the improvement in the state of the AWS patients occurred immediately after treatment; it was observed by the patients and confirmed by the laboratory data. The fact that the medical effect of TET in the proposed conditions unequivocally surpasses that of Relanium, proves that it is a potential and prospective therapeutical method.

The mechanism of the medical effect of the given conditions of TET is presumably as follows: as mentioned earlier, human AWS cerebrospinal fluid and blood plasma are beta-endorphin deficient (Genazzani et al., 1982; Panchenko et al., 1984). On the other hand, it was also observed that TET in the proposed conditions markedly increased the cerebrospinal fluid beta-endorphin content (Ayrapetov et al., 1985). In the present research a considerable increase of blood beta-endorphin content occurred as a result of TET (in the recommended conditions). It turned out that the critical limits of TET parameters activating the endorphinergic brain systems and those producing medical effect in AWS coincide, i.e. the clearly expressed therapeutical effect appears only if that frequency of pulse current is applied, which produces maximal brain beta-endorphin secretion. This supports the assumption that the system of endogenous opioid neuropeptides are involved in the processes, resulting in the medical effect of the proposed TET conditions for AWS treatment. Recently Patterson et al. stated that endorphin mechanisms are involved in the effect of AWS neuroelectric treatment (1984).

The medical effect of endorphins in AWS is connected with their ability to simulate neurotransmission processes, in the first line the catecholamine neurotransmission in the CNS (Anokchina and Kogan, 1984; Najam and Pankseep, 1984). It is particularly important, because, as mentioned before (see introduction), there are the disturbances in the metabolism of catecholamines (especially of dopamine) that are essential in the pathogenesis of AWS.
Thus, in AWS patients and in the predelirium state, the blood dopamine content was increased by 108% and 114% respectively, whereas in the alcohol delirium state the dopamine level exceeded the normal by 358% (Kogan, 1981; Anokchina, 1984). The return to normal of the dopamine level on the 4th-5th-day that we recorded is in good agreement with the dynamics clinically observed, i.e. complete abolition of AWS symptoms at this time. It is also worth mentioning the decrease of blood dopamine concentration 1-2-hours after the first TET, even if not reaching the level consistent with efficient AWS remedy. The medical effect of this form of TET is based on the activation of brain endorphinergic systems, which results in normalization of the disturbed metabolism of biogenic amines in the CNS of AWS patients.

CONTINUED...
Table 1.
Integrate data of AWS expression (percentages from the initial level) in connection with different methods of AWS treatment

<table>
<thead>
<tr>
<th>Form of treatment</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant current + pulse current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(70–80 Hz)</td>
<td>100.0</td>
<td>52.37***</td>
<td>47.63</td>
<td>43.16</td>
<td>13.85***</td>
</tr>
<tr>
<td>Constant current + pulse current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(50–60 Hz)</td>
<td>100.0</td>
<td>86.56***</td>
<td>13.44**</td>
<td>56.69</td>
<td>41.08**</td>
</tr>
<tr>
<td>Constant current + pulse current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(90–100 Hz)</td>
<td>100.0</td>
<td>75.72*</td>
<td>24.28**</td>
<td>62.08</td>
<td>52.30***</td>
</tr>
<tr>
<td>Constant current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>89.54**</td>
<td>10.46***</td>
<td>63.01</td>
<td>56.21***</td>
</tr>
<tr>
<td>Relanium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>69.57**</td>
<td>30.43*</td>
<td>51.26</td>
<td>36.55''</td>
</tr>
</tbody>
</table>

Notes: 1. I, II, III, IV, V—days of AWS treatment.
2. 1—data before treatment.
3. 2—data 1–2 hours after treatment.
3. 3—difference between data obtained before and after treatment.
3. Difference in the obtained data significance evaluated according to Student's test:
   (a) difference of data obtained on days following the day of treatment from that obtained before treatment: + - P<0.05; ++ - P<0.01; +++ - P<0.001.
   (b) difference between the data obtained before and after TET at the same day: * - P<0.05; ** - P<0.01; *** - P<0.001.
<table>
<thead>
<tr>
<th>Metabolites determined</th>
<th>I</th>
<th>1</th>
<th>2</th>
<th>II</th>
<th>1</th>
<th>2</th>
<th>IV–V</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (mg/ml)</td>
<td>0.052 ± 0.003</td>
<td>0.049 ± 0.003</td>
<td>—</td>
<td>0.043 ± 0.002*</td>
<td>—</td>
<td>0.044 ± 0.003*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (mg/ml)</td>
<td>167.6 ± 13.9</td>
<td>156.3 ± 13.6</td>
<td>—</td>
<td>140 ± 6.1</td>
<td>—</td>
<td>132.6 ± 8.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAO, type A (μmol/l·h)</td>
<td>6.1 ± 0.6</td>
<td>6.3 ± 0.6</td>
<td>—</td>
<td>7.6 ± 0.6</td>
<td>—</td>
<td>9.7 ± 1.4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets MAO—type B (nmol/mg·h)</td>
<td>21.4 ± 3.1</td>
<td>23.04 ± 3.0</td>
<td>—</td>
<td>26.5 ± 3.6</td>
<td>—</td>
<td>47.3 ± 5.9***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-endorphin (pmol/l)</td>
<td>5.86 ± 0.72</td>
<td>15.27 ± 2.74**</td>
<td>8.93 ± 0.79*</td>
<td>23.82 ± 3.66***</td>
<td>10.66 ± 0.65***</td>
<td>24.5 ± 1.48***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: 1. I, II, IV, V—days of AWS treatment.
2. 1—data before TET.
   2—data 1–2 hours after TET.
3. Difference in the obtained data, significance evaluated according to Student's test:
   (a) difference between data obtained on days, following the day of treatment and that obtained before treatment:
       +—P < 0.05; ++—P < 0.01; +++—P < 0.001.
   (b) difference between the data obtained before and after TET at the same day: *—P < 0.05; **—P < 0.01;
       ***—P < 0.001.
References


EFFECT OF TRANSCRANIAL ELECTROSTIMULATION OF THE 
OPPIOID SYSTEMS ON THE REPARATIVE PROCESSES IN PATIENTS 
WITH MYOCARDIAL INFARCTION

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Certain synthetic analogues of leucine-enkephalin [natural peptide neurotransmitter] are known to have membrane-protecting action and be able to stimulate the processes of reparative regeneration. For this reason, it was of interest to study a potential beneficial effect of these agents on the course of myocardial infarction (MI). Experimental studies provided evidence that administration of synthetic opioid peptides favored the stabilization of the final volume of necrotic focus and the acceleration of its healing. Opioid peptides were shown to act both via the central nervous system and by a direct effect on the myocardium. Administration of exogenous opioid peptides is also justified by the fact that blood concentration of endogenous opioid peptides is decreased in patients with acute MI.

It is known that the elevation of circulating opioid peptide level in the organism can be achieved not only by the introduction of exogenous opioid peptides but also by the activation of endogenous opioid systems with the use of transcranial electrostimulation (TCES), which leads to a release of opioid peptides, in particular, of beta-endorphin, into the cerebrospinal fluid and blood.

The present work was aimed at studying the course of reparative processes in patients with MI under stimulation of endogenous opioid systems with the use of TCES method.

Material and Methods

Sixty-three patients with primary excessive MI were examined. All patients were admitted to the clinic not later than 6-hr after the beginning of angina attack. Among these patients, 23-persons (20-male and 3-female patients; mean age of 55.6±1.6 yr; anterior MI localization in 70% of cases, posterior localization in 30% of cases) were treated at admittance and subsequently every other of 15-days with TCES in addition to conventional symptomatic therapy. Each session lasted for 25 to 30-minutes, and the strength of current was chosen according to the individual tolerance of each patient (from 6 to 10 mA, 7 mA in average). Frequency (77-Hz) and duration (3.5 to 4-ms of rectangular impulses, as well as the ratio between direct and mean impulse current values (2:1) were maintained at constant levels.

Control group consisted of the remaining 40-patients (34-male and 6-female patients; mean age of 54.5±1.8 yr; anterior MI localization in 77.5% and posterior localization in 22.5% of cases) who received conventional complex symptomatic therapy including, anticoagulants, antiaggregants [preventing clumping], polarizing mixture, vasodilators and anti-arrhythmic agents. The two patient groups were similar in their clinical and anamnestic characteristics.
In order to evaluate the formation of necrotic focus and the development of compensational myocardial hypertrophy (CMH) in patients with anterior MI localization, the method of precordial electrocardioto-photography (ECTPG) [special ECG] described by P. Maroko et al. (1972) and modified by A. V. Vinogradov et al. (1981) was used. The mass of vital myocardium was evaluated according to the total amplitude value of Q waves and QS complexes (ΣSQ+ΣSQS, mm²). The extent of ischemic [low oxygen state] lesion was judged by the total elevation of ST segment above the isoelectric line (ΣST, mm). ECTPG was taken at admittance, after TCES session (in the control group - after administration of the polarizing mixture), on days 2, 3, 5, 10 and 25 of MI development. Simultaneously, using the method of phase analysis of heart activity, the rate of increase in the blood pressure in the left ventricle during the isometric contraction phase (dp/dt, % of the expected value) was determined according to the technique described by A. P. Golikov et al. (1981). Parameters were recorded with the use of Mingograf-4 apparatus (Siemens, FRG).

Collagen metabolism reflecting the formation of post-infarction scar was judged of by the dynamics of plasma protein bound oxyproline (PBO) contents (µmol/l). This parameter was determined at admittance and on days 5, 10, 15, 20 and 25 of MI development according to the technique proposed by A. A. Krel and L. N. Furtseva (1968). Normal PBO level in 22-healthy individuals was 61.5±2.6 µmol/l.

Plasma beta-endorphin concentrations in patients with MI were measured at admittance, after TCES (in the control group – following the administration of polarizing mixture), on days 2, 3 and 5 of MI development using radioimmunoassay with Immuno Nuclear Corp. kit (USA). In a group of 15-patients with CHD and without MI beta-endorphin level was 6.4±0.5 pmol/l.

In all patients cardiac rhythm was monitored daily during the acute MI period. In the cases of repeated angina pain, ST segment elevation and repeated peak of blood creatine phosphokinase (CPK) and CPK MB activities, prolonged course of the disease was ascertained. In order to reveal heart aneurysm, before the discharge all patients were examined using echocardiography or ventriculography. Circulation insufficiency (CI) was designated as being moderate (tachycardia, dyspnoea of less than 24-min⁻¹ and venous stasis in the lungs determined radiographically [X-ray]) or pronounced (tachycardia, dyspnoea of more than 24-min⁻¹ and interstitial or alveolar lung edema as determined by radiography).

**Results and Discussion**

As it is shown in the table, the ΣSQ+ΣSQS value during the acute MI period were virtually similar in both groups; however, on the day 25 of MI development a tendency towards the decrease in size of the necrotic focus could be observed in TCES-treated patients. Thus, on the day 25 the ΣSQ+ΣSQS value was 310.2±35 mm² in the TCES group, whereas in the control group it was 403.2±36.5 mm². Simultaneously, in TCES-treated patients a rapid drop of ΣST could be observed, difference between the two groups being significant on days 10 and 25.
It is known that such dynamics of ECTPG parameters may be associated with the accelerated post-infarction scar formation\(^4\).

Furthermore, in the TCES group, following a period of the decrease in \(\Sigma Rh\), there was an increase in this parameter due to a rise of amplitude of the persisting R waves and their shifting to the place of QS complexes. This fact seems to be associated with the restoration of ischemized cardiomyocyte function and increase in mass of non-infarction portions of myocardium as a result of hyperplasia of intracellular ultra-structures\(^8\).\(^9\).

Additionally, significantly greater dp/dt values were found in the TCES group on days 2 to 10 as compared with those in the control group (see the table). Improvement of heart contractility during the acute period may be brought about by the direct effect of opioid peptides on non-infarction portions of the myocardium\(^6\). During the subacute period, the increase in heart contractility seems to be associated with the accelerated CMH development.

Plasma PBO concentrations in TCES-treated patients with MI were significantly higher, as compared with those of controls, during the period from the day 5 to the day 15 (Fig. 1), that is, exactly on those days when patients were treated with TCES. Increase in blood PBO concentration testifies of collagen metabolism intensification, in particular, of strengthening of collagen synthesis. Such changes reflect the improvement of connective-tissue function and acceleration of the connective-tissue scar formation at the site of necrosis. Thus, in TCES-treated patients with MI, reparative processes become intensified due the accelerated formation of post-infarction scar and the development of CMH.

In order to study more precisely the effect of TCES on the endogenous opioid systems, blood beta-endorphin concentrations were measured in MI patients. It was established that over a period from the day 1 to the day 5 blood beta-endorphin concentrations in patients of the control group were in average 2.9 times lower (Fig. 2) as compared with those in non-MI patients with CHD (\(p <0.01\)). As a rule, blood beta-endorphin level correlated with the severity of patient’s condition, that is, low initial blood beta-endorphin level was associated with MI complications such as pronounced CI, prolonged course of the disease and disturbances of cardiac rhythm.

On the other hand, TCES of the opioid systems resulted in a significant increase in blood beta-endorphin concentrations in patients with MI (Fig. 2). After each next TCES session, beta-endorphin level became 1.8 times higher, in average, as compared with the initial value. Furthermore, stationary blood beta-endorphin level also became higher. Thus, on the day 3 beta-endorphin concentration in the blood of TCES-treated patients, even before the session, was 1.7 times as high as that in the control group, whereas on the day 5 it was 2.4 times as high.

It can be concluded that the TCES-induced increase in blood beta-endorphin concentration is one of the mechanisms underlying the acceleration of reparative processes. Similar effect could be observed following the experimental administration of dalargin, a synthetic opioid peptide. One possible mechanism of dalargin-induced
acceleration of the post-infarction scar formation is that of the stimulation of capillary growth at the site of the scar$^2$.

Improvement of heart contractility due to TCES and the stimulation of reparative processes including the development of CMH were accompanied by a rapid recovery from CI phenomena. Thus, during the period from the day 1 to the day 10 the occurrence of CI in patients receiving conventional symptomatic treatment became 2-times less, whereas in TCES-treated patients it became 4-times less as compared to the initial value. In TCES-treated patients, the incidence of repeated angina pain was also lower.

For instance, on the day 2-repeated pain that required the administration of opioid analgesics was observed only in 13% of patients (compared with 28% in the control group). Prolonged MI course was demonstrated in 8.7% of TCES-treated patients (compared with 30% of controls). By the middle of the day 1, ventricular and atrial extrasystole was revealed in 21.7% and 8.7% of TCES-treated patients respectively, whereas in the control group the corresponding figures were 37.5% and 15% respectively.

Conclusions

1) Transcranial electrostimulation will accelerate the formation of post-infarction scar and the development of compensational hypertrophy of the surviving myocardium, which is accompanied by the improvement of heart contractility. Introduction of this method into the complex therapy for the treatment of myocardial infarction can improve the clinical course of the disease, decreasing the incidence of the signs of circulation insufficiency, repeated angina pain, prolonged course of myocardial infarction and rhythm disturbance.

2) One of the main mechanisms underlying the stimulation of reparative processes during the treatment of patients with myocardial infarction using transcranial electrostimulation is that of the activation of the endogenous opioid system, as determined by the increase in plasma beta-endorphin concentration.

Dynamics of the parameters of precordial electrocardiotopography and heart contractility in TCES-treated patients with MI (M±m).

Charts, Tables, References and Summary follow on next pages
### DYNAMICS OF THE PARAMETERS OF PRECORDIAL ELECTROCARDIO-TOPOGRAPHY AND HEART CONTRACTILITY IN TCES-TREATED PATIENTS WITH MI (Mm)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient group</th>
<th>Time from the onset of MI, days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>1 admittance</td>
<td>after treatment</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>( \Sigma ST, \text{mm} )</td>
<td>I</td>
<td>67.0±8.2</td>
<td>43.8±6.2</td>
<td>54.8±6.0</td>
<td>62.4±5.6</td>
<td>54.7±4.7</td>
<td>42.2±6.1</td>
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<tr>
<td></td>
<td>II</td>
<td>66.3±11.3</td>
<td>36.6±6.0</td>
<td>40.7±7.3</td>
<td>50.7±7.9</td>
<td>44.8±8.3</td>
<td>22.7±5.6</td>
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<tr>
<td>( \Sigma SQ+\Sigma SQ, \text{mm}^2 )</td>
<td>I</td>
<td>157.7±21.3</td>
<td>247.8±27.6</td>
<td>409.5±29.0</td>
<td>410.7±28.9</td>
<td>392.5±28.2</td>
<td>419.9±35.8</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>136.0±31.0</td>
<td>197.3±28.2</td>
<td>376.7±35.1</td>
<td>384.7±39.7</td>
<td>403.5±39.7</td>
<td>393.6±38.1</td>
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<tr>
<td>( LRh, \text{mm} )</td>
<td>I</td>
<td>124.4±10.0</td>
<td>88.9±9.7</td>
<td>33.4±4.8</td>
<td>36.0±5.6</td>
<td>40.6±6.3</td>
<td>40.3±7.5</td>
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<td></td>
<td>II</td>
<td>121.0±25.0</td>
<td>102.0±21.0</td>
<td>74.8±17.9</td>
<td>45.3±13.2</td>
<td>49.2±13.9</td>
<td>77.8±27.0</td>
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<tr>
<td>( dp/dt, % ) of the expected value</td>
<td>I</td>
<td>90.4±5.6</td>
<td>87.6±7.2</td>
<td>58.2±5.5</td>
<td>47.7±5.2</td>
<td>50.7±3.8</td>
<td>65.8±4.3</td>
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<tr>
<td></td>
<td>II</td>
<td>80.2±6.5</td>
<td>102.1±5.4</td>
<td>84.1±4.8</td>
<td>66.7±5.3</td>
<td>71.1±5.4</td>
<td>67.9±4.7</td>
</tr>
</tbody>
</table>

I: control group; II: TCES group; * p<0.05
Fig. 1: Dynamics of plasma PBO contents (µmol/l) in patients with acute MI. Continuous line: MI patients (control), interrupted line: TCES-treated MI patients.

* p < 0.05
Fig. 2: Plasma beta-endorphin concentrations during the course of MI, pmol/l Hatched columns: MI patients (control), black columns: TCES-treated MI patients before session, white columns: TCES-treated MI patients after TCES session

References:


SUMMARY ON NEXT PAGE
Summary

Sixty-three patients with primary excessive myocardial infarction (MI) were examined. Transcranial electrostimulation (TCES) was demonstrated to accelerate post-infarction scar formation, development of compensational myocardial hypertrophy and improvement of cardiac contractility. TCES-induced activation of the endogenous opioid systems was found to be one of the mechanisms responsible for the stimulation of reparative processes in patients with MI. Introduction of TCES into the complex therapy for MI improved the clinical course of the disease, decreasing the incidence of the signs of circulation insufficiency, repeated anginal pain, prolonged course of MI and disturbances of the cardiac rhythm.
ACTIVATION OF THE BRAIN ANTINOCICEPTIVE SYSTEM DURING TRANSCRANIAL ELECTROANALGESIA AND THE ROLE OF OPIOID AND OTHER MEDIATOR MECHANISMS IN THIS EFFECT


As demonstrated by numerous authors, direct electrostimulation of certain median structures in the brain stem leads to a suppression of several motor and autonomic pain responses in animals. These median structures, i.e., the hypothalamic nuclei, the periaqueductal gray matter, the sutureal nuclei, and some others, form the antinociceptive system (ANS), which regulates the conduction of pain impulses at different levels of the CNS, in particular, at a level of the dorsal horns of the spinal cord. Additionally, it has been established that, in various parts of the ANS, the opioid, serotoninergic, and adrenergic mechanisms may play an important role.

The present study was aimed at the determination of whether the brain ANS structures were activated during transcranial electroanalgesia (TEA) and what mediator mechanisms involved in the formation of analgesic effect (AE) were of the foremost importance.

An evidence that, during TEA at a previously designed regimen (Lebedev et al., 1983), activation of ANS structures occurs was provided by experimental autoradiographic determination of activated zones in the brain of rats with the use of $^3$H-glucose. These experimental findings have demonstrated that, during TEA, a significant increase in glucose consumption, which witnessed in an indirect manner the activation of neuron function, occurred in certain nuclei of the hypothalamus and in the periaqueductal gray matter. At the same time, the neuron activation in the medullar nuclei, the thalamus, and the cortical structures secondary to pain stimulation was inhibited.

The TEA-induced activation of the ANS opioid mechanisms has been confirmed by several experimental and clinical findings. Thus, all manifestations of AE and the latter’s autonomic sequelae during TEA could be suppressed in various experimental animal species with low-dose naloxone injections. During TEA, there was a 3- to 3.5-fold increase in beta-endorphin (BE) contents in the midbrain, the dorsal horns of the spinal cord, and the cerebrospinal fluid of rabbits, which was determined by means of radioimmunoaasay.
Similar increase in BE concentration could be observed in healthy volunteers, whereas in patients with pain syndrome, after TEA-induced pain relief, this increase was 5.8-fold in average. A 3.5-fold elevation of BE concentration could be also observed in the blood plasma of healthy volunteers. BE concentration in patients undergoing TEA during surgery was 10 to 15-times as high as the initial one. In accordance with this, BE contents was diminished in the animal hypophysis [pituitary gland], which is known to be the main source of plasma BE. In all these cases, there was a marked correlation between the BE concentration growth value and rate and the degree of AE. Transcranial electrostimulation with other electrical regimens, e.g., with the use of rectangular impulse frequencies of 50 Hz or 100-Hz instead of 77-Hz frequency, could not produce any AE either in healthy individuals or in patients, and, in this case, there was only a slight increase in BE blood plasma concentration.

AE was absent in animals with previously induced tolerance to morphine and was being gradually restored with the reduction of this tolerance. Similarly, AE could not be observed in human individuals with congenital or acquired lack of responsiveness to opiates. Thus, it can be stated that pain responsiveness inhibition induced by TEA involves the ANS opiate mechanisms.

AE did not occur in rats to which 5, 7-hydroxy tryptamin had been injected intracisternally to injure the serotonergic neurons. At the same time, in normal animals, there was preferential increase in serotonin concentration in the cerebrospinal fluid as compared with that in the blood plasma (4 and 2-fold increase respectively). Intracisternally injection of 6-hydroxy dopamine injuring the adrenergic neurons did not lead to any significant changes in the AE. These findings suggest that the essential role in the activation of ANS during TEA belongs to the serotonergic rather than to the adrenergic mechanisms.

It could be hypothesized that the ANS serotonergic mechanisms represent the very unit the pharmacological stimulation of which would allow to regulate the TEA influences upon pain impulse conduction in order to combat pain and its autonomic sequelae.
EVALUATION OF THE EFFECTIVENESS OF A NEW METHOD OF TRANSCRANIAL ELECTROANALGESIA FOR CLINICAL ANESTHESIOLOGY

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A regimen for transcranial electroanalgesia which had been designed on the basis of experimental findings was included for the first time into the complex of anesthesiology aid.

Transcranial electroanalgesia was used in more than 500-cases of heart surgery, including those with extracorporeal [artificial] circulation, as well as lung and gastrointestinal surgery in patients aging from 6-months to 86-years who had a severe concomitant pathology.

It should be noted that the chosen regimen of electrostimulation, while causing the marked and reproducible analgesic effect, did not display any narcotic activity. This circumstance taken into account, hypnogenic drugs were included into the complex of anesthesiology.

Electrostimulation was started immediately after patients’ delivery to the operating room, the total current value measuring from 3 mA to 4.5 mA. The moment of electrostimulation beginning was of great importance since the analgesic effect produced by transcranial electrostimulation (TES) is associated with the increase in beta-endorphin (BE) contents, which would reach the required level only after 15 to 25-min stimulation.

Narcotic induction was performed by means of intramuscular injections of seduxene (0.3 to 0.5-mg/kg), barbiturates (3 to 4-mg/kg), end calypsol (6-mg/kg; used only for children). Tracheal intubation was carried out after administration of depolarizing relaxants at usual doses; muscular relaxation was provided by antidepolarizing relaxants.

Anesthesia was supported by means of TES at the total direct current and average impulse current value measuring from 9 to 24 mA (direct current/average impulse current ratio being 2:1) combined with introduction of nitrous oxide/oxygen mixture (1:1 to 2:1) or with drop by drop infusion of calypsol at the dose of 0.8 to 1.0-mg/kg within one hour, narcotic analgesics being completely excluded. The total current value depended on patient’s age.

TES was stopped 10 to 15-minutes before the end of operation and nitrous oxide and infusion of calypsol were discontinued 5-min before the end of operation, after which patients recovered from anesthesia and the restoration of adequate breathing could be observed, in some cases, without decurarization.
Adequacy of anesthesia was evaluated by measuring the hemodynamic parameters, for which purpose catheterization of radial and pulmonary arteries was performed. Analysis of circulation parameter dynamics (arterial blood pressure, pulmonary arterial pressure, minute circulatory volume, and general peripheral resistance were measured) revealed no significant changes in these parameters throughout the operation. During the operations, which were associated with lung resection, an increase in pulmonary arterial pressure could be observed only during the treatment of the lung root.

In addition, adequacy of anesthesia was evaluated by measuring 17-oxyketosteroids (OKS), adrenalin, and noradrenalin.

During TES (stage of stable anesthesia), 17-OKS concentration out-measured its initial value by 50.4%; However, during operative interventions, including the most traumatic ones, no significant alteration of 17-OKS contents could be observed. One hour after the end of operation and TES, corticosteroid concentration began to decrease to reach the minimal value 6 hr after the end of TES, which was associated with the absence of pain syndrome early in the post-operative period or with the fact that this syndrome was only slightly pronounced.

During the stage of stable anesthesia, TES did not cause any significant increase in noradrenalin (NA) concentration, whereas adrenalin (A) concentration was significantly elevated. This could be due to the increase in blood flow through the adrenal cortex during TES. During the stage of operative intervention, A and NA concentrations became stabilized; it was only during the most traumatic stage when a tendency towards the growth of A concentration could be registered.

TES provided an 11-fold increase in plasma BE contents as compared with the initial value and a 7-fold increase in plasma BE contents as compared with the value which had been registered in the operating room before the initiation of anesthesia. During fluothane anesthesia, the growth of BE concentration was significantly less marked, plasma BE contents being not more than 3-times as great as the initial value. During the operative intervention with TES, BE concentration was maintained at a stable high level, whereas with fluothane anesthesia, this parameter was less stable and changed significantly during the traumatic stages. Discontinuation of TES led to a fall in BE contents by 54% as early as one-hour after the end of TES but it was still 6-times as great as the initial value.

The application TES provided not only the adequate course of anesthesia with complete exclusion of narcotic analgesics and the reduced doses of ataractics and neuroleptics but also the beneficial course of early postoperative period, which was characterized by the presence of residual analgesia. The latter seemed to be due to the elevated BE concentration. The presence of residual analgesia was confirmed by the fact that A and 17-OKS concentrations were relatively low throughout this period.
A direct correlation between the duration of TES and the duration of residual analgesia was revealed. At the same time, the duration of TES and the dynamics of BE concentration decrease were reverse correlated. In addition, contrary to other types of anesthesia, not only immuno-depression did not occur early in the post-operative period, but even an immuno-stimulation could be registered in some cases, which resulted in the decreased occurrence of septic complications.

In conclusion, the above data suggest that anesthesia supplemented with TES provides an adequate course of operative interventions, which are characterized by high traumaticity, and it can be recommended for application in patients at high risk.
NONINVASIVE TRANS-CRANIAL ELECTRICAL STIMULATION OF THE
ANTINOCICEPTIVE SYSTEM OF BRAIN STEM: BIOPHYSICAL,
PHYSIOLOGICAL, NEUROCHEMICAL BASES OF CLINICAL APPLICATION

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The basic purpose of the present investigation consisted of determining of the possibility of activating the antinociceptive system of brain stem with the aid of the electrical stimulation, applied to the surface of the skin of head. For developing this method first of all with the aid of the modified method of nuclear-magnetic- resonance laminography (MRI) optimum direction of current flow was determined, and with the aid of the screening experiments on different forms of animals - optimum characteristics of electric pulses. In the following stages the regions of the brain, which were activated by the transcranial electrostimulation (TES) with the elaborated regime, were determined with the aid of the autoradiographic (absorption [ 3h ] deoksiglucose - DOG) and immunocitochemical (expression of S- PHOS) methods. The neurochemical mechanisms of the antinociceptive system, activated by TES, were investigated with the aid of the radio-immunochemical (b- endorphin, met- enkephalin) and biochemical (serotonin - 5- NT) methods, and also with the aid of the use of pharmacological agonists and antagonists.

According by result, obtained with the aid of NMR, only sagittal direct current can reach antinociceptive system, passing along two intra-cranial ways (spinal liquid of basal cisterns and intraventricular). In the screening experiments were discovered the optimum characteristics of pulse current. In this case dependence " effect - the pulse frequency " and " effect - the pulse duration " reminded of sufficiently sharp quasi-resonance curve. With this type TES increased the absorption DOG in the periaqueductal gray substance and it decreased in the relay nuclei, connected with the transfer of the ascending painful pulsation, and also in the somato sensore cortex. The increased expression C- FOS, caused by immobilization stress, substantially decreased in the different divisions of cortex, the thalamic and hypothalamic nuclei.

TES with the elaborated regime activated mainly endorphin- and the serotoninergic mechanisms of antinociceptive system. A considerable increase of b- endorphin concentration in the structures of brain stem, the dorsal horns of spinal cord, in the cerebro-spinal fluid and the blood, was observed, and met- enkephalin - in the cerebro-spinal fluid. A maximum increase of b- endorphin concentration coincided with the optimum point of quasi-resonance regime TES; the level 5- NT in the cerebro-spinal fluid also rose. In the correspondence by an increase of the concentration of opioid peptide in the cerebro-spinal fluid the level of substance R was decreased, especially during of painful irritation. Effects of TES were blocked by naloxone, 5,7-digidrotriptamin, metergolin and were absent on the background of tolerance to the morphine.
The involution of effects TES was caused by the inhibitors of enkefalainaz (D-leucine, D-phenylalanine), by precursors 5-NT, inhibitors of monoamine oxidase and tryptophan pyrrolase (decrease of the leak/leakage 5-NT of precursor along the kinurenin way). Changes of the effects TES with cholinergic and GABAergic agonist-antagonists were little expressed.

It was shown on the experimental models that TES with the manufactured regime/conditions causes significant analgesia, reduces the value of vasomotor reactions, it activates/promotes the processes of the reparation of the damaged cloths (skin and stomachic epithelium, the hepatocytes, connective tissue, afferent and efferent nerve fibers). The activation of some immune reaction, especially NK-cells, led to the oppression of an increase in different type implanted tumors. Experimental alcoholic abstinence also was removed. All effects were blocked by naloxone and the maximum of their manifestation coincided with the peak of quasi-resonance curve. In accordance with the results of experiments the application OF TES proved to be effective in the clinical practice during the treatment of painful syndromes, neurogenic hypertonia, alcoholic abstinence, stomach ulcers and duodenum, sharp/acute myocardial infarction, sensoneural defective hearing. Clinical effectiveness TES was confirmed by multi-center studies with the application of double blind control in Russia, Bulgaria and Israel. The data, represented in the present report, demonstrate the complete cycle of the successful introduction of the results of the experimental development of the method of transcranial electro stimulation into the clinical practice.
DEVICES FOR NONINVASIVE TRANSCRANIAL ELECTROSTIMULATION OF THE BRAIN ENDOPHINERGIC SYSTEM: APPLICATION FOR IMPROVEMENT OF HUMAN PSYCHO-PHYSIOLOGICAL STATUS.

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Pavlov Institute of Physiology, Military Medical Academy, and Regional Narcological Dispensary, Saint Petersburg; Sklifasovsky Research Institute of Emergency and Center of Extreme Medical Situations, Moscow, Russia; and University of Texas Southwestern Medical Center, Dallas, Texas, U.S.A.

It is well known that deficit of endorphins plays an important role in disturbances of human psycho-physiological status. Previously, we revealed that brain endorphinergic structures have quasiresonance characteristics. On the basis of these data, a method of activation of the brain endorphinergic structures by means of noninvasive and rather selective transcranial electrostimulation (TES) as a kind of functional electrical stimulation (FES) was elaborated. New models of TES devices (TRANSAIR) were developed for indoor and outdoor usage. To increase the efficacy of TES, the frequency modulation according to normal distribution in the limits of the quasiresonance characteristics was put into operation. The blind and placebo-controlled (passive and active placebo) study was produced to estimate the TES effects on stress events and accompanied psycho-physiological and autonomic disturbances of different intensities on volunteers and patients in the following groups: everyday stress and fatigue; stress in regular military service and in field conditions; stress in the relatives of those lost in mass disaster; posttraumatic stress (thermal burns); and affective disorders in a postabstinence period. Some subjective verbal and nonverbal tests and objective tests (including heart rate variability) were used for estimation of the initial level of psycho-physiological status, which changes after TES sessions. It was demonstrated that fatigue, stress, and other accompanied psycho-physiological disturbances were significantly improved or abolished after 2-5 TES sessions. The TES effects were more pronounced in cases of heavier disturbances. In conclusion, activation of the brain endorphinergic structures by TES is an effective homeostatic method of FES that sufficiently improves quality of life.

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SECTION 2: HISTORICAL REVIEW OF CES/TES TECHNOLOGY
CRANIAL ELECTROTHERAPY STIMULATION AS A TREATMENT FOR ANXIETY IN CHEMICALLY DEPENDENT PERSONS.
Richard Schmitt, PhD, Thomas Capo, BS, and Ehrin Boyd, MD: Alcoholism: Clinical and Experimental Research, 10(2) March/April 1986

Cranial electrotherapy stimulation (CES) is reported to be effective treatment for anxiety, a major presenting symptom among chemically dependent patients. In this study, 40 inpatient alcohol and/or poly-drug users were given CES or sham CES in a double blind design. An additional 20 patients served as normal hospital routine controls. Dependent measures of anxiety were the Profile of Mood States, the Institute for Personality and Ability Testing Anxiety Scale, and the State/Trait Anxiety Index. CES-treated patients showed significantly greater improvement on all anxiety measures than did either control group. There were no differences in response between older and younger patients, or between the primary drug or alcohol users. No placebo effect was found on any of our measures. It is concluded that CES is a clinically significant addition to the treatment regimen for this patient population.

ELECTRICITY IN PAIN MANAGEMENT

For more than thirty years there has been a revival of electrotherapy in the treatment of pain. Analgesia by electrical current is now based on transcutaneous or percutaneous nerve stimulation, deep stimulation, posterior spinal cords stimulation, and transcutaneous cranial stimulation. **EFFICACY:** It is now scientifically proven that electrostimulation of certain peripheral fibers and of different structures of the central nervous system plays an undeniable role in filtration and control of painful messages. However, precise indications are a prerequisite. Transcutaneous electrical nerve stimulation is only effective if it acts on neurogenic pain, only if the nerve pathways to be stimulated are superficial, and only if the conduction pathways between the area of stimulation and the superior centers are intact. Neurosurgical electrostimulation techniques should only be proposed after failure of simple therapies. **INDICATIONS:** For acute pain, electrostimulation of certain intracerebral structures and transcutaneous cranial electrostimulation may be indicated. Clinicians have a multitude of electrostimulators at their disposal but generally, the parameters recommended for their use have no serious scientific basis. The selected electrical neurostimulator must provide effective nerve stimulation without causing lesions. Electrostimulation could be considered as an adjunct to medicinal treatment for pain relief.
TRANSCUTANEOUS CRANIAL ELECTRICAL STIMULATION INCREASES THE POTENCY OF NITROUS OXIDE IN HUMANS


The potency, amnesic, and postanesthetic analgesic effects of transcutaneous cranial electrical stimulation (TCES) were evaluated during N2O anesthesia in 120 unpremedicated patients, prior to urologic or general surgical operations. The patients were divided into six groups of 20 each with respect to what concentration of N2O in oxygen they were allowed to breathe (75, 62.5, and 50%), and whether they were or were not stimulated with TCES. Recordings of heart and respiratory rates, systolic arterial blood pressure, and minute ventilation were made prior to and after 20 min of N2O, and one minute later following application of a Kocker clamp to the upper inner thigh for one minute. The presence or absence of movement during the painful stimulus, memory of the painful stimulus, and postanesthetic pain at the clamp site (20 min after anesthesia) were also evaluated. Patients who received TCES had significantly lower incidences of movement, memory of the painful stimulus, and postanesthetic pain at the stimulation site at each N2O concentration than patients not getting TCES. TCES did not alter circulatory and respiratory dynamics prior to painful stimulation and prevented an increase in arterial blood pressure during painful stimulation in patients receiving 50% N2O. These data indicate that TCES significantly increases the analgesic potency of N2O and probably also the depth of anesthesia.

TRANSCUTANEOUS CRANIAL ELECTRICAL STIMULATION DECREASES NARCOTIC REQUIREMENTS DURING NEUROLEPT ANESTHESIA AND OPERATION IN MAN


The influence of transcutaneous cranial electrical stimulation (TCES) on fentanyl requirements was evaluated in 50 patients undergoing urologic operations with pure neuroleptanes themia (droperidol, diazepam, fentanyl, and air oxygen) with (group I) or without (group II) simultaneous TCES. All patients had silver electrodes (three) applied between the eyebrows and behind each mastoid process and attached to a 167-kHz current generator. Current was delivered only to group I. The wave form was a complex nonsinusoidal, nonsquare wave pattern which was applied intermittently in a 3-msec-on 10-msec-off sequence. All patients had anesthesia induced with droperidol (0.20 mg/kg IV), diazepam (0.2 mg/kg IV), and pancuronium (0.08 mg/kg IV), and, after tracheal intubation, had anesthesia maintained with fentanyl in 100-microgram intravenous increments every 3 minutes whenever and as long as systolic arterial blood pressure and/or heart rate were greater than 20% of control (preanesthetic induction) values. Fentanyl requirements averaged 6.1 +/- 0.5 and 7.9 +/- 0.4 microgram/kg/min for a mean total dosage of 9.0 +/- 0.9 and 12.5 +/- 0.8 microgram/kg for the entire operation.
in groups I and II, respectively. These differences between groups were statistically significant (p less than 0.05). The data demonstrate that TCES augments the analgesic effects of fentanyl and thus reduces fentanyl requirements during urologic operations with neuroleptanesthesia.

META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS OF CRANIAL ELECTROSTIMULATION. EFFICACY IN TREATING SELECTED PSYCHOLOGICAL AND PHYSIOLOGICAL CONDITIONS

To clarify the diverse published results of cranial electrostimulation (CES) efficacy, we conducted an extensive literature review that identified 18 of the most carefully conducted randomized controlled trials of CES versus sham treatment. For the 14 trials that had sufficient data, we used the techniques of meta-analysis to pool the published results of treating each of four conditions: anxiety (eight trials), brain dysfunction (two trials), headache (two trials), and insomnia (two trials). Because studies utilized different outcome measures, we used an effect size method to normalize measures which we then pooled across studies within each condition. The meta-analysis of anxiety showed CES to be significantly more effective than sham treatment (p < .05). Pooling did not affect results that were individually positive (headache and pain under anesthesia) or negative (brain dysfunction and insomnia). Most studies failed to report all data necessary for meta-analysis. Moreover, in all but two trials, the therapist was not blinded and knew which patients were receiving CES or sham treatment. We strongly recommend that future trials of CES report complete data and incorporate therapist blinding to avoid possible bias.

IMMEDIATE INFLUENCE OF TRANSCRANIAL ELECTROSTIMULATION ON PAIN AND BETA-ENDORPHIN BLOOD LEVELS: AN ACTIVE PLACEBO-CONTROLLED STUDY

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 beta-endorphin levels were measured before and after treatment. RESULTS: beta-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 beta-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 beta-endorphin blood levels.

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**THE EFFECTS OF TRANSCRANIAL ELECTROSTIMULATION ON THE ADAPTIVE STATE**
Markina LD. Kratinova EA.. [Clinical Trial. Controlled Clinical Trial. Journal Article]

The effects of transcranial electrostimulation on medical students with different types of adaptive responses (training, activation, stress, reactivation), levels of reactivity, and psychophysiological and autonomic status were studied. These experiments showed that transcranial electrostimulation was effective for subjects with adaptive responses of the training and activation types but not in those with stress combined with marked vagal tension. Transcranial electrostimulation facilitated improvements in psychophysiological parameters of the students and increased the level of body reactivity.

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**IMAGING OF CURRENT DENSITY AND CURRENT PATHWAYS IN RABBIT BRAIN DURING TRANSCRANIAL ELECTROSTIMULATION**
Joy ML. Lebedev VP. Gati JS.. [Journal Article. Research Support, Non-U.S. Gov't]
IEEE Transactions on Biomedical Engineering. 46(9):1139-49, 1999 Sep.

A magnetic resonance imaging (MRI) method was used for a noninvasive study of current density (CD) and current pathways (CP’s) inside the skull during transcranial Electrostimulation in rabbits. The transcranial impulse current directions studied were those previously used in transcranial electric treatment either sagittally or bilaterally. MRI data were collected from slices perpendicular to the direction of current application. In these slices, only the perpendicular component of the CD was measured. Computer methods for accurate topographic mapping of the main areas with high CD and for reconstruction of CP’s are described.

It was revealed that current applied on the head sagittally passed mostly through the cerebrospinal fluid in the basal brain cisternas connected in series, and through the anterior horns of the lateral ventricles, foramina of Monro, ventrocaudal part of the third ventricle, aqueductus, and fourth ventricle. Possible connections between these CP’s are suggested. Bilaterally applied current passed through the brain and skull core more
diffusely without concentrations in cisternas and ventricles. The results of the present study suggest an explanation for the observation that sagittally applied current more effectively stimulates brain structures with antinociceptive function and elicits more pronounced analgesic effect.

THE EFFECTS OF ELECTROSLEEP ON INSOMNIA REVISITED

Ten subjects who had suffered from sleep onset insomnia for a minimum of 2 years participated in a double blind study of the effects of electro-sleep on this disorder. This paper reports a 2-year follow-up of these subjects. Of the five subjects who received 24 live treatments, four appeared to be able to fall asleep with little difficulty and to awake feeling moderately to very well rested. Only one appeared to have relapsed during the 2-year-no-treatment period. Of those receiving sham treatment four were having quite a bit of difficulty falling asleep but three of the five awoke feeling moderately well rested. Although the number of subjects is small, the trends appear consistent with the interpretation that sleep habits were improved for most of the real treatment subjects and for few of those receiving sham treatment.

TRANSCUTANEOUS CRANIAL ELECTRICAL STIMULATION (TCES):
A REVIEW 1998.

The Transcutaneous Cranial Electrical Stimulation (TCES) technique appeared at the beginning of the 1960s and is aimed to act at the level of the central nervous system. The current, composed of high frequency pulses interrupted with a repetitive low frequency, is delivered through three electrodes (a negative electrode placed between the eyebrows while two positive electrodes are located in the retro-mastoid region). Due to the characteristics of the current delivered, shortcomings encountered with previous electrical stimulation techniques are avoided. The main property of TCES is to potentiate some drug effects, especially opiates and neuroleptics, during anesthetic clinical procedures. This potentiation effect permits drastic reduction of pharmacological anesthetic agent and reduces post-operative complications. Animal studies performed with TCES demonstrated that this stimulation releases 5-hydroxy-indol-acetic acid and enkephalins. Despite numerous clinical and animal studies performed with this technique for several decades, TCES mechanisms are not completely elucidated but results obtained without undesirable effect are encouraging signs to continue investigations of this particular technique.
TRANSCRANIAL ELECTRICAL STIMULATION WITH HIGH FREQUENCY INTERMITTENT CURRENT (LIMOGE’S) POTENTIATES OPIATE-INDUCED ANALGESIA: BLIND STUDIES

Louis Stinus, Marc Auriacombe, Jean Tignol, Aimt Limoge and Michel Le Moal. . Pain, 42 (1990) 351-363

Transcutaneous cranial electrical stimulation (TCES) with high frequency (166 kHz) intermittent current (100 Hz; Limoge current) has been used for several years in cardiac, thoracic, abdominal, urological and micro-surgery. The main benefits are a reduced requirement for analgesic drugs, especially opiates, and a long-lasting postoperative analgesia. We have confirmed these clinical observations in rats using the tail-flick latency (TFL) test to measure pain threshold. TCES was not found to modify the pain threshold in drug-free rats, but it potentiated morphine-induced analgesia (systemic injection). To obtain a maximal effect, the stimulation must be initiated 3 h before the drug injection and be maintained throughout the duration of its pharmacological action. TCES potentiation was found to depend on the dose of the drug, the intensity of the current and the polarity of electrodes. These findings were confirmed by blind tests of the efficiency of TCES on several opiate analgesic drugs currently used in human surgery (morphine, fentanyl, alfentanil and dextromoramide). The analgesic effect of these 4 opiates (TFL as % of baseline without or with TCES) were respectively: 174%, 306%; 176%, 336%; 160% 215%; and 267%, 392%. The results were obtained not only after systemic opiate treatment, but also after intracerebroventricular injection of morphine (10 ng; analgesic effect 152%, 207% with TCES) suggesting that TCES potentiation of opiate-induced analgesia is centrally mediated.

THE EFFECTS OF ELECTROSLEEP ON INSOMNIA REVISITED

Rosalind Dymond Cartwright, PhD and Marc F Weiss, MA. Brief Communication:. The Journal of Nervous and Mental Disease, 161(2) 134-137, 1975

Ten subjects who had suffered from sleep onset insomnia for a minimum of 2 years participated in a double blind study of the effects of electro-sleep on this disorder. This paper reports a 2-year follow-up of these subjects. Of the five subjects who received 24 live treatments, four appeared to be able to fall asleep with little difficulty and to awake feeling moderately to very well rested. Only one appeared to have relapsed during the 2-year no-treatment period. Of those receiving sham treatment four were having quite a bit of difficulty falling asleep but three of the five awoke feeling moderately well rested. Although the number of subjects is small, the trends appear consistent with the interpretation that sleep habits were improved for most of the real treatment subjects and for few of those receiving sham treatment.
Cranial Electrotherapy Stimulation (CES) has a growing history of applications in rehabilitation medicine in the United States dating back to early 1970. As a recognized non-drug treatment of anxiety, depression and insomnia, CES gained its first major application in the field of addiction treatment and rehabilitation. By the mid 1980s research was showing additional important uses of CES in the treatment of closed head injured patients, and in paraplegic and quadriplegic patients. The most recent research is showing CES to be highly effective in the management of chronic pain patients. It may be elevating the pain threshold due to its stress reducing effects when anxiety and depression are reduced below clinical levels. Modern theorists of a pain neuromatrix in the cerebral cortex may provide an additional basis for understanding CES mechanisms in the control of pain related disorders.

The practice of using electrical stimulation for pain control began centuries ago. However, renewed interest in electroanalgesia is related in part to a better understanding of the physiologic basis of pain perception and transmission, as well as to the efforts of researchers interested in finding alternatives to the traditional opioid and nonopioid analgesic drugs. Electrical stimulation has been applied directly to the spinal cord, deep brain centers, peripheral nerves, and to the traditional Chinese acupoints, in an effort to improve the management of acute and chronic pain. This report examines the current scientific evidence supporting the use of electroanalgesia in pain management.
SECTION 3: PRESENTATION OF NEXALIN CLINICAL TRIAL RESULTS TO INTERNATIONAL SCIENTIFIC COMMUNITIES
LONG-TERM PAIN RELIEF VIA TRANSCRANIAL ELECTRO STIMULATION (TES) USING THE NEXALIN DEVICE

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Background and Aims:
Activation of the brain’s antinociceptive system using TES provides short-term reduction of pain. The aim is to determine the possibility of long-term pain reduction using TES with the Nexalin Device.

Methods:
N=94 subjects with hip and/or knee Osteoarthritis. This prospective, randomized, double-blind, placebo controlled trial contained two treatment arms: Arm 1 received 7 daily 40minute Nexalin treatments; Arm 2 received 7 daily 40minute placebo treatments. Assessments included pain level (PL), subject’s global self assessment (SGA), walking test (WT) and physician’s assessment (PA) – all utilizing visual scales. Assessments were completed during the 3 weeks baseline period, the 7 day treatment period, and the 12 week follow up period.

Results:
PL decreased in Nexalin group compared to placebo: after 7 treatments - p=0.0000, after 2 weeks - p=0.0000, after 14 weeks - p=0.0180.

PL during WT decreased in Nexalin group compared to placebo: after 7 treatments - p=0.0011, after 2 weeks - p=0.0080, after 14 weeks - p=0.0397.

SGA in Nexalin group compared to placebo: after 7 treatments - p=0.0072, after 2 weeks - p=0.0093. PA in Nexalin group compared to placebo: after 2 weeks - p=0.0069.

Percent of subjects with No or Mild pain: before treatment - 0%, after 7 treatments - Nexalin 70%, Placebo 38% (p<0.0018); after 2 weeks - Nexalin 64%, Placebo 39% (p<0.016); after 14 weeks - Nexalin 62%, Placebo 45% (p<0.07)
Conclusions:

Nexalin Therapy is an effective treatment for the reduction of long-term pain associated with Osteoarthritis of the hip and/or knee.
In contrast to deep brain stimulation, the information concerning transcranial electrostimulation (TES) for treatment of Parkinson’s disease (PD) is limited. TES is based on the activation of opioidergic systems of the brain. Disturbances in the production of endogenous opiates and serotonin could be one of the mechanisms underlying the development of PD. Presently; TES is widely used to treat depression, insomnia, and pain. The aim of this study was to evaluate the efficacy of the TES via “NEXALIN” device for treatment of PD.

Twenty patients with mild and moderate PD were enrolled in a 5 week open label trial. Repeated clinical assessments, testing with UPDRS, and “Up and Go” were conducted during baseline (2 weeks), treatment (7 consecutive days; each session: 40 minutes, average current 15 mA) and follow up (2 weeks). All patients maintained their regular pharmacotherapy.

Statistical and clinical improvements were noted in decreasing symptoms of hypersalivation, depression, and bradykinesia (p<0.05). Also observed were improvements in postural unsteadiness, stiffness, carriage, sleep, and mood. Decreases were noted in freezing when waking, facilitation of cutting of food and writing, and pain levels. The analysis of the “Up and Go” demonstrated decreased time (p<0.0001). Number of steps reduced after 7 sessions and the first week of follow up (p<0.0001). At final follow up the number of steps returned to the base level.

No side effects were registered.

The results of treatment of PD via the “NEXALIN” device proved some effectiveness of TES and could be the basis for future trials.
NONINVASIVE ACTIVATION OF BETA-ENDORPHINERGIC SYSTEM OF THE BRAIN USING "NEXALIN" DEVICE FOR TREATMENT OF OSTEOARTHRITIS PAIN

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Purpose:

Research supports that the direct activation of the Beta-Endorphinergic Systems (BES) could successfully decrease the level of pain experienced. The "NEXALIN" design uses a proprietary wave form (US Patent 6,904,322 B2), based on a quasi resonance frequency of 77.5 Hz. This frequency was confirmed in many prior Russian trials and studies, as being key to stimulating the increase in concentration of beta-endorphins in the brain, spinal fluid and blood (SU Patent #1522500). The aim is to prove the possibility of decreasing pain caused by osteoarthritis (OA) by using transcranial electrostimulation (TES) via the "NEXALIN" device.

Methods:

The study was multi-centered, randomized, double-blind, and placebo-controlled. The study population consisted of 211 patients who had been diagnosed with OA of knee and/or hip, had a pain history of at least three months, and scored 4 or more on the Visual Score for Pain Assessment. The "NEXALIN" groups received 7 daily TES session of 40 minutes, 15 mA (root mean square); the placebo group received no stimulation using a visually identical device.

Assessment methods: pain level (PL), patient global self-assessment (PGA), walking test (WT), physician’s assessment (PA) - all utilizing visual scales. Assessments were performed prior to treatment, during the treatment series, and at the 1 year follow-up assessment.
Results:

After 7 treatments: PL decreased in the "NEXALIN" group 57%, placebo 24% (p<10-9), WT 54% and 30% (P<10-4); PGA and PA increased respectively 47% and 25% (P<0.04), 44% and 32% (P<0.03).

After 2 weeks: PL decreased in the "NEXALIN" group 40%, placebo 21% (p<10-4), WT 42% and 30% (P<0.01); PGA and PA increased respectively 29% and 25% (P<0.66), 42% and 30%(P<0.01).

Statistically analysis also showed decreasing of PL in the "NEXALIN" group during at least 6 weeks.

The number and type of side effects were equivalent in both groups, with quantities in placebo exceeding active.

Conclusions:

"NEXALIN's" TES device, realized through activation of BES, provides significant and prolonged decrease in pain associated with OA.
PAIN IN EUROPE, ISTANBUL, 2006

TREATMENT OF OSTEOARTHRITIS PAIN VIA TRANSCRANIAL ELECTROSTIMULATION OF ANTINOCICEPTIVE SYSTEMS (ANCS) OF THE BRAIN USING THE NEXALIN DEVICE

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Background and Aims:

Activation of ANCS of the brain using a quasy resonance frequency of 77.5 Hz was proven effective in clinical and experimental studies. The Nexalin design uses a proprietary wave form based on 77.5 Hz. The result is Nexalin provides stimulation without sensation under electrodes (US Patent 6,904,322 B2).

The aim is to determine the possibility of decreasing pain caused by osteoarthritis (OA) by using the Nexalin design.

Methods:

200+ patients with OA of knee and/or hip joints comprised the groups. The study was randomized, double-blind. The NEXALIN groups received 7 daily treatments of 40 minutes, 15 mA (root mean square); the placebo group received no stimulation using a visually identical device. Assessment methods: pain level (PL), patient global self-assessment (PGA), walking test (WT), physician’s assessment (PA) – all utilizing visual scales. Assessments were performed during three weeks prior, one week during, 2 weeks after the completion of treatment.

Preliminary Results:

After 7 treatments: PL decreased in the NEXALIN group 57%, placebo 24% (p<10-9), WT 54% and 30% (P<10-4); PGA and PA increased respectively 47% and 25% (P<0.04), 44% and 32% (P<0.03).

After 2 weeks: PL decreased in the NEXALIN group 40%, placebo 21% (p<10-4), WT 42% and 30% (P<0.01); PGA and PA increased respectively 29% and 25% (P<0.66), 42% and 30% (P<0.01).

The number and type of side effects were equivalent in both groups, with quantities in placebo exceeding active.
Conclusions:

NEXALIN provides significant decrease of pain associated with OA and improvement in general condition.
Aim of Investigation:

A newly developed cranial electrostimulation (CES) device, NEXALIN, was tested for efficacy of pain relief in subjects suffering from osteoarthritis.

Methods:

The study was a prospective, double-blind, randomized, and controlled. The safety and effectiveness of two active Nexalin waveforms were compared to a sham treatment. A total of 140 subjects from three separate sites completed the study. The subject population consisted of adult men and women who had objective evidence of osteoarthritis, had experienced pain for at least 3 months, and self-assessed their level of pain of at least 4 out of 10 on the Visual Scale for pain. The active groups received daily 40 minute treatments of CES for 7 days, using either the symmetric or asymmetric NEXALIN waveform. The sham group received 7 treatments using an identical device that was programmed to provide no CES. Because there is minimal or no sensation with either form of active treatment, subject blinding was not compromised.

Assessments were performed during a baseline (two weeks), during the week of treatment, and at least one week after the completion of active or sham treatment.

Results:

Pain levels decreased 34% in the sham group, 48% in asymmetric and 51% in the symmetric group (p<0.03 between symmetric and sham groups); and decreased by at least 75% in 9%, 28.6% and 23.8% of patients respectively. Contrast tests for % improvement showed a statistical difference only between symmetric and sham groups. Statistically significant decrease in rescue medication usage was noted only in the symmetric group. Physician's assessments also noted a significant improvement in condition only in the symmetric group, as compared to sham group (p<0.01).

Conclusions:

Treatment with the symmetric waveform of the NEXALIN led to a significant decrease of pain intensity and decrease in analgesic rescue medication usage when compared to
sham treatment. NEXALIN can be an effective alternative to pharmacological methods of pain treatment.

Citation:


TEMPORARY PAIN RELIEF USING TRANSCRANIAL ELECTROTHERAPY STIMULATION: RESULTS OF A RANDOMIZED, DOUBLE-BLIND PILOT STUDY.

Katsnelson Y, Khokhlov A, Tsvetkov V, Bartoo G, Bartoo M.

Kalaco Sci., Inc., Scottsdale, AZ, USA.

Results of a randomized, double-blind pilot study indicate that transcranial electrotherapy stimulation may be an effective treatment for the temporary reduction of pain in osteoarthritis patients. Presently, the predominant method for pain management is medication. One very different approach is the application of micro- to milliamp current applied to specific areas of the head, resulting in a release of endogenous opioids from pain management regions of the brain. For the pilot study, 64 subjects suffering from osteoarthritis of the knee and/or hip were enrolled. For two weeks prior, then during and after treatment, subject pain was self-assessed using the visual scale (VS). In addition, subjects were globally assessed by a physician. All subjects, device operators and physicians were blinded as to whether subjects were treated with an active or sham device. Data collected from the study indicate both a decrease in VS pain scores and a significant improvement ($p = 0.05$) in physician assessment in subjects treated with active devices compared to those treated with the sham device.
Methods

The evaluation of psychological status during treatment of pain syndrome was accomplished using Luscher’s test as a tool of early diagnostics psychological and somatic stress, and the mathematical analysis of cardiac rhythm (MACR) for the evaluation of processes of regulation and adaptation.

The treatment of pain syndrome was accomplished using transcranial electrostimulation (TES) via “TESA” device (Kalaco Scientific, USA).

Results

In the first group (n=15) tests were performed before and after one 30 minute session of TES; in the second group (n=12) – before and after 30 minute sessions for the duration of 5 days.

1. Intensity of pain level (PL) was determined on a visual analog scale (10 grades); the man being 5.95. After the first session the intensity of PL decreased by 45% and continued to decrease every following day. At the end of the treatment, the PL was 1.75 (P<0.05).

2. In 75% of subjects of both groups, a steady decrease (p<0.05) of the factor of uneasiness (FU) was marked; in 23% tendency to the decreasing of FU and only in 2% did the level of FU not change.

3. A correlation was found between PL and FU and reverse correlation between PL, FU and factor capability to work.

4. The level of parameters of MACR (adaptation, vegetative regulation, central regulation, psycho-emotional conditions) was increased (p<0.05) after the first session and continued to normalize until the end of TES course.

Conclusion

“TESA” brings about not only an analgesic effect but also the normalization of psychological status.
‘TESA’ IS A NEW DEVICE FOR TRANSCRANIAL ELECTROSTIMULATION

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The study’s goal was the evaluation of the analgesic effect of “TESA” (Kalaco Scientific, USA) - the new device for transcranial electrostimulation (TES).

“TESA” has been investigated in a group of 27 patients (14 men, 13 women) with different pain syndromes. Pain level (PL) was determined on visual analog scale (10 grades) and averaged 5.95 before treatment. The mathematical analysis of cardiac rhythm (MACR), parameters of central hemodynamics, activity of cellular enzymes, protein level and the plasma’s electrolytes were used to evaluate the patient’s condition.

- TESA decreased PL by 44.9\% after the first session and by 56.9\% over the course of treatment.
- The average duration of analgesic effect after the first application was 12.0 hours. The repeated stimulation provided steady analgesic effect.
- The positive influence of TESA on the expressiveness of stress reaction was shown in the significant decrease of blood glucose when initially elevated.
- Parameters of MACR (adaptation, vegetative regulation, central regulation, psycho-emotional conditions) were increased after the first session and continued to normalize until the end of TES’s course (p<0.05).
- Before TES all patients had initially high level (p<0.05) of vegetative equilibrium (VE), adequacy of regulation’s processes (APR) and stress index (SI), which indicated a disturbance of the relationship between sympathetic and parasympathetic systems. After the first treatment VE, APR and SI were significantly decreased. The normalization of relationship continued for the duration of the whole TES’s course (p<0.05).
- No considerable influence of “TESA” on normal parameters of central hemodynamics, cellular enzymes, protein and plasma’s electrolytes is revealed.