METABOLISM OF BIOGENIC AMINES DURING THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME BY TRANSCRANIAL ELECTRIC TREATMENT

A. Ja. GRINENKO,* E. M. KRUPITSKIY,* V. P. LEBEDEV, Δ Ja. S. KATSNELSON, †
G. F. KARANDASHOVA,* K. A. MOSHKOV, § V. V. BULJON, §
V. A. ILLIUUCHINAI and JU. S. BORODKIN§

*Leningrad Regional Centre for Prevention and Treatment for Addiction;

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-squattings) 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 pre-delirium 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>
<thead>
<tr>
<th>Form of treatment</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
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<tbody>
<tr>
<td>Constant current + pulse current</td>
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<td>(70-80 Hz)</td>
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<td>(50-60 Hz)</td>
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<td>86.56++</td>
<td>13.44++</td>
<td>56.69</td>
<td>41.08***</td>
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</tr>
<tr>
<td>(90-100 Hz)</td>
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<td>75.72*</td>
<td>24.28++</td>
<td>62.08</td>
<td>52.30***</td>
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</tr>
<tr>
<td>Relanium</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. I—data before treatment.
   2—data 1–2 hours after treatment.
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 2.
Biochemical studies in patients of the major group during AWS stoppage

<table>
<thead>
<tr>
<th>Metabolites determined</th>
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<th>2</th>
<th>I</th>
<th>2</th>
<th>IV–V</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>
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<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>
</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>
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<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>
</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>
</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


*Studies continue on the next page*
THE EFFECT OF TRANSCRANIAL ELECTROSTIMULATION OF THE BRAIN OPIOID STRUCTURES ON THE PERIPHERAL NERVE REGENERATION IN RATS


Abstract
The effect of transcranial electrical stimulation of the brain opioid structures on the sciatic nerve regeneration after complete transection and subsequent microsurgical restoration of the nerve was studied. Electrostimulation appeared to accelerate the regeneration of sensory and motor fibers of the sciatic nerve. Participation of endogenous opioid peptides in the regeneration of peripheral nerves is discussed.

Introduction
Recent studies revealed that opioid peptides and their synthetic analogues contributed to the acceleration of reparative processes in different tissues, in particular, in the nervous tissue. This was shown with reference to neurite growth in the tissue culture upon addition of opioid peptides as well as upon exogenous introduction of opioid peptides into the organism of animals with injured peripheral nerves.

Objective of this work was to study the influence of transcranial electrostimulation of the brain-stem antinociceptive structures, which will cause intensive release of endogenous opioid peptides, on the regeneration of injured nervous fibers.

Methods
Experiments were carried out using 30-male rats weighing from 200 to 250-grams. Regeneration of the sciatic nerve was studied after transection of the nerve at the mid-femoral level and connecting of its ends to each other with epiperineural microsurgical stitch, which usually results in a successful regeneration of the injured nerve. Animals were operated under hexenal anesthesia (0.25-g/kg) using microsurgical technique, that is, with operational microscope, atraumatic needle with supramide thread (10/0 to 11/0) and microsurgical instruments.

After operation, one animal group (15-rats) underwent electrical treatment with the use of electrodes inserted subcutaneously at the forehead and behind the ears. Regimen of stimulation that had had been developed previously was used, which included a combination 0.8 mA direct current with impulse current of 0.4 mA, with the frequency of 70-Hz and duration of 3.0 to 3.5-ms. These parameters of stimulation provided the maximum analgesic effect and were optimal ones for the acceleration of wound healing. Animals were thus treated for 1-hr a day with 3-day intervals over a period of 2-weeks. Another group of 15-operated animals was used as a control group.
Rat’s foot reinnervation [restoration of function by re-growth or grafting] with motor nervous fibers was estimated with the use of vestibular motor test, that is, reflex parting of the toes of the hind foot upon quick lowering of the animal (Fig. 1). This test is widely used in the rat experiments for the study of regeneration process in the motor nervous fibers of the injured sciatic nerve\textsuperscript{11}. Regeneration of the sensory nervous fibers was studied using the method of impulse activity lead from microbundles of the sciatic nerve during mechanical stimulation of the foot skin\textsuperscript{1, 10}.

**Results**

Vestibular motor test revealed a characteristic cramping-together of the toes at rest after operation, which persisted also upon quick lowering of the animal\textsuperscript{11} (Fig. 1). The first sign of the restoration of motor activity, that is, drawing-aside of the 4\textsuperscript{th} and 5\textsuperscript{th} toe, could be observed 5.0±1.0-days after operation in the experimental group, whereas in the control group it could be seen 9.0±1.5 after operation. There was a difference between the groups both in time by which the reflex had reappeared and in the character of its development. In the experimental group the reflex, once having been restored, could be then observed constantly, whereas in the control group it had become stable only by the day 13 after operation.

Impulse activity of sciatic nerve fibers was registered for 30-days after operation. First impulse reactions to a strong mechanical stimulation (pinch or prick) were found 14±1 d after operation in electrostimulation-treated animals and 19±1 d - in controls. At those terms, induced impulse activity could, be demonstrated when a very small area of the foot skin at the heel was stimulated (Fig. 2, 1). High irritation threshold level and limited reception area at the proximal part of the foot provided an evidence that it was only an initial stage of foot reinnervation with sensory fibers of the injured sciatic nerve. Thirty days after operation, receptive response area expanded in the experimental animals to the entire surface of the foot skin, being concentrated in the central part of the foot (Fig. 2A, 3). In the control group receptive area, though being also spread over the entire foot surface, remained rarefied, and the field responsive to mechanical stimulation was situated more proximally as compared with that in the experimental group (Fig. 2B, 3).

**Discussion**

Our findings suggest that transcranial electrical stimulation will accelerate the regeneration of injured peripheral nerves. Due to the methods employed in this study, our consideration is restricted to the initial stage of foot reinnervation with motor and sensory nervous fibers. It has been determined that electrical stimulation accelerates the reinnervation of the foot with motor and sensory fibers in average by 30\% and 25\% respectively.

According to the findings of histological examination of the foot skin, no specialized receptor structures could be observed during the early stage of regeneration (up to 30 d after operation) while only thin, poorly myelinized nervous plexuses could be demonstrated\textsuperscript{10}. 


Foot responsiveness to mechanical stimulation during this period seems to be associated with the ability of regenerating nervous fibers themselves to respond to mechanical stimulation. It is known\(^7\) that transcranial electrostimulation at the regimen proposed by us will activate the brain antinociceptive structures and is associated with a significant increase in the concentration of opioid peptides in the cerebrospinal fluid and blood. As it was demonstrated earlier\(^1\), dalargin, an opioid peptide, being administered systemically, accelerated the process of peripheral nerve regeneration. Thus, not only endogenous but also exogenous opioid peptides stimulate regeneration process in peripheral nervous conductors.

Data obtained from the experiments with tissue culture provide evidence that opioid peptides exert a neurite-stimulating and trophic influence on the nervous tissue and accelerate proliferation and migration of the glia. Electrophysiological studies revealed the existence of opioid receptors in the membrane of the sensory neurons in the spinal ganglia\(^{12}\). It could be suggested that the effect of opioid peptides on the regeneration of injured periphery nerves consists of several components as follows: the influence on the neurons' resistance to trauma, the stimulation of neurite growth and the acceleration of proliferation of glial elements and their penetration into the zone of growth. Additionally, the beneficial influence on the regeneration of nervous fibers could be exerted by the opioid peptide-induced normalization of microcirculation and lymph flow\(^9\) as well as by the immunomodulating effects of opioid peptides\(^3\).

Our findings provide evidence that the method of opioid system electrostimulation is a promising approach to the treatment of injured peripheral nerves in humans. Moreover, this method is already in clinical use for the achieving of analgesia\(^4\).

Fig. 1: Vestibular motor reflex in rat after injury of the right sciatic nerve.
Fig. 2: Impulse activity of nervous fibers of the sciatic nerve during mechanical stimulation of the foot skin 15 (1), 20 (2) and 30 (3) days after operation

A. experimental group; B: control; a: response oscillograms (upper trace: impulse activity, lower trace: stimulation mark); b: receptive area localization in the foot skin.

References:


Studies continue on page 103
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APPLICATION OF TRANSCRANIAL ELECTROSTIMULATION TO THE TREATMENT OF PRIMARY DEFORMING OSTEOARTHRITIS


Primary deforming Osteoarthrosis (osteoarthritis) (PDOA) characterized by generalized damage to the joints brings considerable economic detriments to the community because of its high occurrence in the population, which leads to a significant short and long-term disablement (Benevolenskaya and Brzhezovski; 1988).

The course of PDOA as well as the markedness and extent of arthralgia [joint pain] and functional damage to the joints are significantly influenced by vascular tone disorder resulting in poor blood supply to the joints, which was evidenced by thermoasymmetry [measures temperature variation] above the joints as measured by electrothermometry, thermovision and rheovasography (Zabolotnykh et al., 1976, 1982; Zabolotnykh and Tarasov, 1983; Zabolotnykh and Balabutkina, 1985; Hohmeister, 1982). Therefore, for the treatment of PDOA, besides chondroprotectors exerting their effect only after long-term administration (Feitelevich et al., 1983), means of generalized effect are required which could ameliorate blood supply to the joints. Application of non-steroid anti-inflammatory agents is not expedient since they inhibit prostaglandin synthesis, which deteriorates blood supply to the cartilage, and proteoglycan production, which promotes the development of PDOA; moreover, these agents not infrequently lead to complications (Guobis and Yushenaytene, 1981; Astapenko, 1986; Greiling, 1983). Local physical therapy is of no great use for the treatment of PDOA because of multiple arthropathy [disease of the joints] and combined complications and can be effective only after a long-term course.

It is known that general analgesia with marked analgesic after-effect can be achieved with the use of transcranial electrostimulation (electroanalgesia) (Lebedev et al., 1985), which is also associated with a considerable rise in beta-endorphin level (Airapetov et al., 1985). Taking into account the facts that serum beta-endorphin levels are lowered in patients with PDOA (Denko et al., 1982) and that endogenous opiates play an active role in the regulation of circulation (Hand et al., 1986), it seems likely that transcranial electrostimulation would be useful in PDOA treatment.

Our work was aimed at studying the efficiency of transcranial electrostimulation for simultaneous treatment of numerous joints in patients with PDOA during deterioration of the disease or the development of complications.

Transcranial electrostimulation (TES) was performed via cutaneous metal frontal and retromastoidal [behind the ear] electrodes provided with 10 to 16-layer white-flannel pads moistened with tap water, with the use of a modified version of “Electronarcon 1” apparatus.
At first, direct current gradually growing up to 1 to 3 mA within 1-15-min was applied; later on, rectangular impulse current (impulse frequency of 77-Hz; impulse duration of 3.5-ms; strength of current reaching 5 to 6 mA) was used until the achievement of analgesia or, in the absence of arthralgia at rest, until the appearance of a feeling of hydrophilous [moisture] pad slipping down towards the eye-brows. During a first, test session when the tolerance to the procedure was determined, TES lasted 15-min; subsequent sessions lasted 30±2-min each. The course of treatment consisted of 7-TES sessions performed daily or with one-day intervals. If necessary, the course was prolonged and consisted of 10-sessions.

Treatment efficiency was judged of by the overall index of pain syndrome markedness which included the intensity of arthralgia, joint and functional index values and the intensity of crunching and paresthesia, expressed in points, before and after TES course. In addition, before and after each TES session skin temperature was measured with a TPEM-1 electrothermometer at five symmetric points (on the earlobes, at paravertebral points at level of the 7th-cervical vertebra and over the wrist, knee and ankle joints). Data on temperature changes were used for the calculation of thermoasymmetry reduction or increase and temperature rise or fall at the appointed points during each TES session. Before and after each TES session pain quantitative criteria were also examined using a visual analogous scale. After the course of treatment, total values of thermoasymmetry reduction and temperature rise as well as pain relief according to the visual analogous scale were determined in percent of baseline values.

Course of treatment which in average consisted of 7-TES sessions was complete in 39-patients with PDOA. Overall session number was 275. Most patients underwent a single TES course, whereas three patients received 2-courses each and one more patient – 3-courses. There were 20-male and 19-female patients in the examined group. Patients' age ranged from 19 to 62 yr; 87% of patients were able to work. Seventeen out of 39-patients (44%) worked under unfavorable conditions. Duration of the disease ranged from 2 to 45-yr. Slowly developing manifest PDOA forms were diagnosed in 76.3%, while 23.7% had rapidly developing PDOA forms. In the majority of patients (95.2%) pathological process was sub-compensated. All patients had generalized lesions of the joints of the upper and lower limbs and the spine. Maximum pain syndrome in the knee joint was found in 34-patients.

Fibrous nodules could be revealed in 28-patients; however only 12 of them suffered from pain in the distal finger joints. PDOA complications included mostly periarthritis (knee-joint bursitis in 24, shoulder-joint bursitis in 6, elbow-joint bursitis in 7 and ankle-joint bursitis in 7 patients). Reactive synovitis of the knee joints was diagnosed in 3-patients while reactive synovites of the minor hand and foot joints were found in 3-patients. PDOA was complicated by root syndrome in 21-patients. Multiple complications were revealed in 19-patients.

A stable beneficial effect was observed in 35-patients (89%) After treatment, pain at rest as well as after exercise disappeared. In patients with deteriorated PDOA pain was simultaneously stopped in many joints of the limbs and spine and a stable remission could be achieved after 7-sessions.
In the cases of PDOA complicated by periarthrosis or reactive synovites, besides the pain relief in many joints, the reduction of periarthrosis, synovitis or root syndrome manifestations could be obtained, all these manifestations subsequently disappearing completely without any additional treatment, as judged by follow-up observations. The achieved effect improved with each next TES session. The changes in general pain were estimated according to the visual analogous scale (VAS) averaged for all patients before and after each TES session. Pain relief with time proceeded in parallel with thermoasymmetry regression. Significant decrease in thermoasymmetry with each next session can be seen, this decrease being maximum pronounced after the 7th-session. Simultaneously with the decrease in pain and thermoasymmetry, a rise in temperature could be observed at tested skin points after each TES session It was also showed, the reduction in general pain estimate according to VAS, related to the day of treatment and expressed in percent of the initial value. Temperature rise as well as the decrease in general pain estimate were statistically significant. It was showed the changes in total clinical picture of PDOA during the course of treatment. A significant decrease in arthralgia intensity, joint and functional index values and thermoasymmetry could be observed Changes in clinical characteristics in 39-patients after TES treatment are indicated as percent of initial values in the Table.

Beta-endorphin concentrations were studied before and after TES treatment. Mean beta-endorphin concentration before treatment was 9.11±1.03-pmol/l, whereas after the first session it rose to 21.05±3.02-pmol/l and by the end of the course it was stabilized at 16.9±2.77-pmol/l.

Follow-up examination was performed in 28-TES-treated patients. The after-effect lasted for more than one year in 23-patients, 11-months in 2 and 4 to 5-months in 3-patients.

Rise in temperature over the tested skin points in parallel with the thermoasymmetry regression and decrease in pain as measured by VAS after each TES session as well as after the whole course provided an evidence for the improvement of blood supply to the joints, i.e. for the pathogenetic nature of TES therapy.

Pronounced therapeutic effect of TES can be explained by several pathogenetic mechanisms. Taking into account the data obtained by Denko et al. (1982) and Ayrapetov et al. (1985) as well as our own observations on the increase in beta-endorphin concentration following TES, one possible mechanism may be seen in the activation of endorphin complex in the brain-stem and spinal-cord antinociceptive systems.

Liberation of receptors from pain stimulation, be it only for a period of TES performance and its after-effect, (8 to 10-hr) breaks the pathological chain, provides rest to receptors, which allows to restore their beta-endorphin releasing activity, and triggers therapeutic pathogenetic process. This is also favored by the cessation of the constant pathological impulses from the damaged joints and/or periarthral tissues which otherwise causes and supports vascular spasm, promotes microcirculation disturbances and development of degenerative processes in the joints. In addition to the analgesic effect, TES seems to normalize the central regulation of vascular tone. This hypothesis is supported by the decrease in thermoasymmetry, the latter reflecting a dis-coordination in the activity of the vasomotor center, a pair organ that works synchronously under physiological conditions (Kurshakov and Pressman, 1969).
Therefore, blood supply to the joints can be improved even at the moment of TES session, which is confirmed by the reduction of thermoasymmetry and the rise in temperature over the joints and earlobe after each TES session and after the complete course, as measured by electrothermometry.

Application of TES allowed significant reduction in the duration of treatment due to a simultaneous arresting of complications in a number of joints. Never before could we achieve such a success in the treatment of deteriorated uncomplicated, to say nothing of complicated one, PDOA in 7 to 10-days. TES can be used in arthrological clinics, under common outpatient conditions. This method does not require the application of any medication or other means of physical therapy and is therefore free of their side effects. Contraindications for TES include severe brain pathology, severe rhythm disturbance paroxysms and marked functional disorders of the central nervous system and inner organs.

Data on the decrease of thermoasymmetry paralleling the elimination of pain in PDOA patients during TES sessions, which was accompanied by a significant rise in temperature over the joints, provide additional evidence for the important role played by the disturbances in vascular tone and blood supply to the joints in the development of arthralgesic syndrome in PDOA, and support the necessity of including preparations that could improve blood supply to the joints and normalize vascular tone of the organism into the treatment protocol for the patients with PDOA.

Table: Changes in PDOA clinical characteristics after TES treatment.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Changes, % of initial values M±m</th>
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<tr>
<td>General pain estimate (VAS)</td>
<td>-33.55±4.64</td>
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<tr>
<td>Total pain syndrome index</td>
<td>-49.17±4.15</td>
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<td>including:</td>
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<tr>
<td>joint index</td>
<td>-53.66±4.72</td>
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<td>functional index</td>
<td>-45.86±4.89</td>
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<tr>
<td>pain intensity</td>
<td>-55.28±4.85</td>
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<td>Thermoasymmetry reduction</td>
<td>-20.43±3.79</td>
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Legends to the Figures from the paper “Application of Transcranial Electrostimulation to the Treatment of Primary Deforming Osteoarthrosis” by A. N. Tarasov, I. I. Zabolotnykh, V. A. Zabolotnykh and V. P. Lebedev:

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TRANSCRANIAL ELECTROTHERAPY IN REHABILITATION OF OSTEOARTHRITIS PATIENTS.

L. A. Komarova, V. V. Kyrianova, I. I. Zabolotnih, V. A. Zabolotnih

Osteoarthritis (OA) is one of the widespread ailments of the joints. An important pathogenically factor of this disease is the disruption of blood supply to cartilage and sub-cartilage tissue in the bone, resulting in the destruction of articular cartilage [covers articular surfaces of bones] and degenerating processes in epiphysis of connecting bones. These changes are accompanied by a disruption in vascular tonicity, by a degradation of microcirculation, and by a reactive inflammation in the general area of the joints. Complications of OA are most frequently treated by a lengthy use of non-steroid anti-inflammatory medicines (NSAIM), which are relatively frequently accompanied by severe side effects, such as complications of stomach and duodenum ulcers, bleeding, etc. Also, NSAIM disrupt the synthesis of vasodilating prostaglandins, thereby worsening the blood supply to cartilage, chondrocyte [cartilage cell] exchange, and the creation of proteoglycans. An even greater amount of complications occur as a result of the use of glucocorticoid solutions, which is signified by osteoporosis of bones, increases arterial pressure, bleeding ulcers, etc.

Currently, in the course of the rehabilitation of OA patients, physical therapy is being included frequently. Considering the generalized character of joint ailments during OA, such as intensive pain syndrome and the disruption of reparative processes in bone and cartilage tissue, for the treatment of patients we selected a method of stimulation with impulse-based electrical current on the brain, which affects the central nervous system and through it acts on the main symptoms of pathological process.

The method was researched in St. Petersburgh Institute of Physiology by V. P. Lebedev et al. Called Transcranial Electrostimulation (TES), wherein the stimulation is achieved via the use of the machine “Transair”, which supplies rectangular-shaped impulse current with a fixed frequency of 77-Hz and the duration being 2.5-ms with direct current. The methodology of treatments involves the application to the skin of metal electrodes with pads, located in the area of the forehead above the eyebrows (cathode) and split (anodes) on each mastoid [behind the ear]. The duration of the procedure is 30-min. The duration of treatment is 8 – 10-sessions, held daily or every other day.

The authors of the TES methodology carried out multiple experiments on animals, and also used this methodology in clinical situations. It’s established that with a fixed frequency of 70-77-Hz, TES results in an increase in production of peptides, specifically of beta-endorphin, which is accompanied by a lengthy analgesic effect, especially in patients with severe pain syndromes.

The secretion of said peptides into the blood, as a result of TES, assists in the acceleration of regeneration and normalizes hemodynamics [blood circulation]. Endogenic opioids mobilize the creation of vasodilatory prostaglandins and improve localized blood flow, to a certain extent eliminating the disruption of vascular tonicity of central genesis. These effects can be important in treating patients with OA.
In our studies, we treated 39 patients, mainly with OA of the knee joints, aged 19-69, with the duration of disease 2 – 45-years. These patients were treated strictly with TES. The effectiveness of treatment was judged as follows: by clinical dynamic of illness, including via the intensity of pain in the joint, which were judged with a numerical system of 1 to 3 using the methodology developed by I. I Zabolotnih (2); the numerical amount of pain sensitivity, judged with the use of a visual scale (VS); the level of sensitivity during palpation of joints determined in amounts of joint index (Doyle et al 1980); the functionality of joints determined with the use of functional index (N. I. Trafimov et al, 1980) which was judged by the ability of the patients to reproduce the most common movements made in everyday life. The evaluation of beta-endorphin levels was performed via a radio-immunological method (7).

During the treatments, the temperature of skin tissue was measured on five symmetrical points (on level C7, on wrist, knee and ankle joints and on the earlobe) after which, the level of thermo symmetry and its absolute levels were determined. The level of concentration of beta-endorphins in blood was important in the explanation of effect mechanisms. All the above-mentioned objective factors were studied before and after treatment, and also before and after each session the temperature of skin was taken on the five said points and the numerical amount of pain sensitivity was determined via VS.

After the treatment with TES, the condition of patients improved significantly. Stable positive effect was noted in 35 people, or 89%. After treatment, the patients no longer experienced pain during sleep, or after an extended time of inactivity, and also during and after movements. In patients with complications of OA, there was a decrease in periarthritis, amount of synovitis, or radiculitis. During the specific study of pain syndromes, a definitive weakening of such was found, since after treatments the intensity of pain levels was decreased by 55.3%. Joint index was lowered by 53.7%. The level of pain sensitivity determined by VS was lowered by 33.5% as compared to initial data. Pain sensitivity was also lowered after each session of TES. The functionality of joints was improved.

Before the treatment, the concentration of beta-endorphin was 9.11+/-1.03 pmol/l, and after completion, there was noted a significant increase in concentration of beta-endorphin by 7.8 pmol/l and it stabilized at the level of 16.91+/-2.77 pmol/l. Next fact is very important: immediately after the end of the first session, the concentration of beta-endorphin increased on average by 11.94 pmol/l (resulting in 21.05+/-3.02 pmol/l).

The increase in the concentration of beta-endorphin after the first session and after course (8-10-sessions) of TES points to a very intensive activation of endogenous opioid system of the brain. Activation of opioid mechanisms of the brain explains the analgesic effect of this method of treatment.

After the treatment, skin temperature rose by an average of 1 - 2 degrees C, and thermo-symmetry was lowered. The regress of thermo-symmetry was also noted at the end of successive sessions. These changes indicate an improvement in the process of blood flow to the joints, especially in microcirculation. Apparently, the increase in the creation of neuro-peptides, by blocking efferent pain impulses, which result in vessel spasms, results in an improvement in localized blood circulation.
It’s also important to note the normalization of the condition of vessel-moving center as a result of TES, which is signified by the lowered level of arterial pressure in patients with neurocirculatory dystonia by hypertension type (3), and, indirectly, by the decrease in thermo-symmetry of skin.

Therefore, the use of TES resulted in the general improvement of the condition of patients with OA, proven by the data of catamnesis [follow medical history] of 28 of 39 people. The positive effect remains for more than a year in 23-patients, 11-months in 2, and 4 – 5-months in 3. The mechanisms of therapeutical [curative] effect of TES in connection with OA, are connected primarily to the stimulation of endorphin structures of the brain and the attainment, because of this, of a strong analgesic effect, and also to the improvement in blood circulation to the affected joints, largely via processes of microcirculation, which decreases trophic [nutrition] disruptions and slows the progress of degenerative-dystrophic changes of the joint.

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A NEW METHOD OF TRANSCRANIAL ELECTROANALGESIA

Theoretical Basis and Practical Evaluation, Scientific and Practical Conference
Leningrad, March 1987

(Abstracts)

Foreward

Does there exist any effective transcranial electroanalgesia? Despite the long history exceeding 60-years of development, which had begun with the investigation by French physiologist S. Leduc (1902), this question, paradoxically as it is, should not yet be regarded as a rhetorical one. It is worth mentioning in this connection, that, within much shorter time intervals, a variety of new analgesics as well as neuroleptoanalgesia, ataractanalgesia, and other methods of pain combating have become readily available for clinical practice and are now widely used without any problems and hesitations. However, transcranial electroanalgesia, which was considered to be a younger sister to electroanesthesia is still rather an issue to be investigated than a method, which could be widely employed, whereas an item of electroanesthesia has been already removed from the agenda.

During this long history, the investigation into the field of transcranial electroanalgesia underwent numerous rises and falls. At present, judging by the proceedings of periodical international congresses concerning electrosleep and electroanesthesia, there is rather a decrease in attention to this problem. Perhaps only in the USSR and in France are such investigations continued constantly, and the proceedings of the present Conference provide a certain evidence for the expansion of these investigations in our country. Thus, the question about the existence of transcranial electroanalgesia is not a rhetorical one. There is a real problem to be solved.

What is the reason for such a recurrent growth in interest to transcranial electroanalgesia? One possible explanation is that of an a priori attractiveness of electroanalgesia due to some properties which are thought to be intrinsic to this method, i.e., easy and rapid achieving of timely analgesia, deliberately controlled duration and reversibility of the effect, and the absence of any side-effects as well as the exclusion of toxic and, particularly, of allergic sequelae of analgesic drug therapy which could, if not completely abolished, be significantly reduced. At present, there is an evident discrepancy between our desires and reality, which provides a ground for further scientific research.

During the long period of investigation into the field of transcranial electroanalgesia, a wide variety of electro-stimulation regimens differing in several parameters was studied, the effectiveness of each new regimen being usually highly estimated by its author, although this could not be proved by subsequent trials in most cases.
Recently, it has been even stated that specific current parameters are not so much important. Perhaps it is only fair in regard to a nonspecific effect of current. Not without reason did S. Leduc, in his turn, suggest to apply “an initial current impulse” by far surpassing in its value the usual limits but providing subsequent effect achievable with currents of therapeutic range.

Proceedings of the present Conference reflect a different approach to the investigation into transcranial electroanalgesia. Joint experimental studies performed by physiologists (I. P. Pavlov Institute of Physiology, USSR Academy of Sciences) together with anesthesiologists (All-Union Scientific Research Institute of Pulmonology, USSR Ministry of Public Health) with the use of instrumentation produced by engineers working in Leningrad have demonstrated that, in order to achieve a marked and reproducible primary analgesic effect, it is of principal importance to use an electric regimen with strictly defined parameters. Subsequent investigation has led to a conclusion that transcranial electrostimulation with similarly strictly defined parameters will stabilize the central regulation of circulation and normalize the regulation mechanisms underlying a variety of functions and processes. In the course of experiments, it could be determined that these effects are based on the selective influence exerted by the chosen electric parameters upon the certain brain structures which perform a key role in the stabilization of homeostasis. Eventually, this new finding reflects a relationship between the selectivity of stimulation of certain brain structures and the transcranial electrostimulation parameters.

It might be suggested that transcranial electrostimulation with adequate parameters would make it possible to affect selectively some other chosen brain structures. At any rate, it is already clear now that transcranial electrostimulation at the suggested regimen acts via both stimulating and checking components, which allows the inhibition of the adverse effects and to enhance the desirable ones. This is demonstrated, for example by the fact that galvanic component of the proposed electric regimen is capable of suppressing a titanic [tonic contraction] effect produced by impulse component and, at the same time, of potentiating the latter’s analgesic effect. This means that, under given conditions, the stimulating effect induced by impulse current in the elements of motor regulation is inactivated whereas the selective influence on a defined group of the subcortical structures which belong to the antinociceptive system is enhanced.

Curriculum of the present Conference was designed according to its scientific and practical objectives. This is also reflected by the sequence of abstracts published in this volume. Part I represents experimental data, which provide a basis for the choice of regimen for the proposed method of transcranial electroanalgesia and elucidate the mechanisms underlying the analgesic effect. Parts II and III include the data concerning the clinical assessment of this method's effectiveness in anesthesiology and in arresting various pain syndromes. Part IV, the closing one deals with the results of clinical and experimental studies which provided a strong evidence that the effect of transcranial electrostimulation is not restricted to mere analgesia but is rather more expanded, stimulation with optimal current parameters being of extreme importance also in these cases.
In conclusion, it seems important to stress an obvious, which is, in our opinion, to be demonstrated by the present Conference that physical methods of treatment can be effective only when based on accurate and quantitative experimental data. Only under this condition was it possible to determine the real limits for the method of transcranial electroanalgesia to yield desirable clinical effects.

[signed]

V. P. Lebedev, MD,
USSR State Prize Laureate

Studies continue on page 117
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TRANSCRANIAL ELECTROANALGESIA

V. P. Lebedev

Transcranial electroanalgesia (TEA) is a method of electrical stimulation of the cranial tegument that can cause analgesic condition or reduce pain. It is understood that electric current passes through the skin, soft tissues of the head and the skull, finally affecting the brain. The term “transcranial electroanalgesia” is used to designate not only the resulting condition but also the procedure itself. Therefore, similar condition or procedure are not infrequently referred to as “central electroanalgesia” (CEA) or “transcerebral percutaneous electrostimulation” (TPES). It should be admitted that the term “TEA”, though indicating the nature of stimulation, the site of current’s application and the final effect, is obviously an incomplete one since it does not reflect the mechanism of action. However, it is more informative in its structure compared with some other widely used terms such as “local anesthesia” or “infiltration anesthesia”. The term “CEA” seems to be too extended since it may include the stimulation of both the brain and the spinal cord, both via the tegument and by a direct effect. The term “TPES”, though indicating a certain mechanism of action, does not elucidate the object of percutaneous and transcerebral stimulation as well as the purpose of this stimulation. Thus, this term also appears to be somewhat inexact since it may be used to designate any stimulation of the head skin, including physiotherapy, or electroshock treatment.

As it will be demonstrated below, the phenomenon in question could be given a descriptive designation of “percutaneous transcranial electrical stimulation of the brain-stem antinociceptive system”.

There is purposely no emphasis on the analgesic effect in this description since analgesia is coupled with a number of other important and beneficial effects.

From Electronarcosis Towards Electroanalgesia

Attempts to influence the brain by means of stimulating the head’s surface with different kinds of electric current had been made since the end of the 19th-century. They were based on the results of physiological studies by E. Dubois-Reymond and E. Pfluger, according to which electrical stimulation may not only induce but also inhibit the activity of responsive tissues. A certain contribution to the research into this field was made by the experimental studies of the inhibitory effect of direct current on unicellular organisms as well as on fish and amphibians.

Purposeful research into the problem began with the work by S. Leduc (1903) who achieved narcosis-like condition in experimental animals by stimulating them with interrupted direct current via electrodes applied to the forehead and the loin. This effect was further supported by the results of a self-experiment, which was successful, in Leduc’s own opinion, but had to be discontinued by Leduc’s colleagues in view of appearing life-threatening complications.

The possibility of achieving electronarcosis in humans attracted the attention of many investigators, however, each time they thought to have approached this goal, it would turn out to be unattainable.
Since the beginning of the 60s, it gradually became obvious that transcranial electrical stimulation can lead to a marked analgesic effect which may be used as a component of anesthesia (electropharmacoanesthesia) and as a means for the treatment of pain syndromes. Investigation into this field was carried out clinically and experimentally by a number of authors in our country (Kuzin M. I. et al., 1966; Chaskov V. I., 1972, Persianiov L. S. et al., 1978; Shloznikov B. I., 1985) and abroad (Limoge, 1975). The essence of all these studies consisted in the selection of optimal regimen of electrical stimulation, which could, without any complications result in a marked and reproducible analgesic effect.

**Characteristics of Electrical Parameters and Instruments Used for TEA**

During the study of TEA, patients were treated at first with impulse current of constant parameters (Leduc’s currents). With the progress in electronic technology, a tendency emerged towards variation of electrical parameters within a wide range. Of late, attention is once again drawn to the application of stable and constant parameters of stimulation for individual patients.

At different stages of investigation the following kinds of electric stimulation were mainly studied and used: continuous impulse stimuli, sinusoidal currents, interfering currents, combination of continuous impulse stimuli with additional galvanic component varying within a narrow range, groups of high-frequency bipolar impulses (Limoge’s currents) and combination of continuous impulse stimuli or groups of high-frequency pulses with additional galvanic component varying within a rather wide range.

Steady commercial production of instruments for TEA in our country is connected with apparatuses such as Electrosleep, Electronarcon-1, EA-12-01 and LENAR.

Electrosleep and Electronarcon-1 as well as their analogues, EA-12-01, LENAR etc., which appeared later on, represent, in fact, one common class of instruments which produce continuous impulse stimuli, with varying frequency and duration, combined with additional galvanic component varying within a narrow range.

Limited usage of instruments such as Electrosleep, assigned for achieving sedative and hypnotic effects, in TEA is due mainly to a specific way of electrode application, which significantly restricts the range of stimulus amplitude variation.

Fronto-occipital application of electrodes realized with Electronarcon-1 and its analogues allows [the use of] impulse stimuli and a galvanic component of greater amplitudes, which may result in unpleasant feelings in patients and requires protective measures to prevent skin burns.

At present, those instruments may be considered to be the most effective ones for TEA that allow using impulse current of fixed frequency and duration. Only [now have] such regimens received sufficient experimental support and clinical evaluation.

Basing on the studies by Limoge, in France an Anesthelec [tradename] apparatus has been designed which allows to obtain groups of bipolar high-frequency impulses of fixed frequency. Impulse groups themselves are also of fixed frequency and duration. The absence of additional galvanic component and the peculiarity of produced stimuli reduce unpleasant feelings under the electrodes and prevent skin burns in patients.
A method proposed by M. I. Kuzin et al. (1984) should be regarded as a promising one. This method is a modification of Limoge’s technique that allows to spread the effect of electrical stimulation over a greater portion of the brain tissue. The use of another method ascertained the high efficacy of combined application of rectangular impulses of fixed frequency and duration with galvanic component exceeding in its amplitude the mean impulse current value (Lebedev V. P. et al., 1984). The similarity in electrical characteristics between these two methods should be noted, that is, similar frequencies of rectangular impulses or impulse groups as well as similar durations of each impulse or group.

**Experimental Substantiation of Optimal Electrostimulation Regimen and the Possible Mechanism of TEA**

Regimen that is optimal for TEA should cause the most profound and reproducible and analgesic effect with minimum possible current value. Large-scale screening with the use of quantitative evaluation of the analgesic effect has resulted in a conclusion that such an effect can be achieved with the impulse current of critical parameters as follows: frequency and duration of rectangular impulses or impulse groups should be 77±2-Hz and 3.5 to 4-ms respectively. When any other frequency or duration values are employed, with a given current amplitude, the analgesic effect becomes significantly reduced. Galvanic component significantly increases the analgesic effect caused by impulse current and reduces the probability of any side-effects on a condition that the ratio between direct and mean impulse currents is maintained at the level of 2:1 (Lebedev V. P. et al., 1983). Such current produces a greater analgesic effect than that achieved with Limoge’s current with equal impulse group frequency and duration but with 10-times as large value of mean impulse current (Kovalev M. G., 1987).

The importance of maintaining the critical regimen of impulse current to obtain analgesia was confirmed by clinical observations (Vanevski V. L., Grinchenko S. A., 1987; Shmonin A. V., 1987). It is this. criticity that distinguishes the TEA regimens described above from all those studied during more than 80-years of research into the electronarcosis and electroanalgesia.

It has been established that during application of such TEA regimen a selective stimulation of the antinociceptive system of the brain stem occurs, the activity of which is ensured, in the first place, by the endogenous opiate mechanism.

Evidence for the fact that it is the selective activation of antinociceptive structures that is induced by such TEA regimen was provided by the results of experimental autoradiographic examination of activated zones of the brain using 2-deoxy-α-1=3H-glucose (Lebedev V. P., 1986). Activation of antinociceptive structures such as the dorsomedial hypothalamic nucleus, the periaqueductal gray matter and the raphe nuclei was accompanied by the inhibition of neurons in those structures that conduct pain impulses (relay nuclei of the medulla and the thalamus as well as somatosensory area of the cortex).

Activation of opiate mechanisms of the antinociceptive system was evidenced by the fact that TEA was responsive to naloxone; by the rapid increase in beta-endorphin concentrations in animal and human blood plasma and cerebrospinal fluid, as determined...
by radioimmunoassay during TEA, as well as by the increase in beta endorphin concentrations in the animal antinociceptive structures (Kuzin M. I. et al., 1984; Airapetov L. P. et al., 1985). This hypothesis was further supported by the results of experimental autoradiographic study of the competition between TEA-induced endogenous opioids and 2-125I-morphine, a mu-opioid receptor ligand (Airapetov L. P. et al., 1987). Especially pronounced displacement of labelled ligand was found in the antinociceptive structures, thus confirming the selectivity of the effect produced by the chosen TEA regimen. Furthermore, uneven release of endogenous opioid peptides and their unequal dependence on the intensity of stimulation were demonstrated.

The mechanisms of TEA described above are very close to the mechanisms of analgesia induced by the direct stimulation of the antinociceptive system. Therefore, the investigation in-to the details of TEA mechanisms should be based on the data obtained from the study of stimulation analgesia.

Further experimental studies allowed [us] to determine that, within the same narrow parameter range, TEA can exert an effective stabilizing influence on the central regulation of circulation (Katsnelson Ya. S., 1985) and normalize the regulation of a number of functions and processes such as wound healing (Ilyinski O. B. wt al., 1987) and nonspecific resistance (Gritskevich N. A. et al., 1987). Characteristically, all these TEA-induced effects are maximally pronounced when the same critical impulse current parameters are used and can be also inhibited by naloxone.

Besides the TEA regimen that selectively affects the antinociceptive system, several other regimens are still used in the clinical practice. These methods differ from each other in their electric parameters and have not been sufficiently based on the experimental findings (Persianinov L. S. et al., 1978). A certain analgesic effect reported by clinicists (Medical Doctors] may be associated, in this case, with non-specific mechanisms induced by electric current. In any case, no analgesic effect can be precisely demonstrated in the experimental studies with such stimulation regimens. A number of hypotheses were proposed in order to explain the nature of nonspecific effects (vascular, cellular, and reflex ones). All these hypotheses are now of only an historical interest.

Clinical Application of TEA

TEA is used in the clinical practice for many different purposes. In this review, we shall consider only those aspects of clinical application of TEA that are based on critical electric parameters selectively stimulating the antinociceptive system.

Research into this field is still in progress, yet the high clinical efficacy of this procedure is obvious.

TEA as a component of anesthesia. Introduction of TEA into the anesthesiology complex allows [us] to reduce significantly the doses of general anesthetics as well as to minimize (with Limoge’s currents) or exclude (with rectangular impulses of fixed frequency with large direct component) the administration of narcotic analgesics.
The main objective of the use of general anesthetics in this case consists in the disconnection of consciousness. Analgesic effect is clearly demonstrated by the hemodynamic stability at the most traumatic episodes of the operation (Katsnelson Ya. S., 1985; Shloznikov B. B. I., 1985, Grinchenko S. A., 1986). Biochemical data also support this finding, revealing the dynamics of stress hormones. Opioid character of analgesia indicated by a sharp raise of beta-endorphin concentrations in plasma and cerebrospinal fluid. This effect is more marked when rectangular impulses with direct component is used as compared to that achieved with Limoge’s currents (Katsnelson Ya. S., Leosko V.A., 1987).

Application of TEA is especially beneficial during major surgery in patients with concomitant disorders such as allergic problems, hepatic failure etc. TEA may be administered not only to adults but also to children and aged patients.

List of operations during which TEA was successfully used is very long and includes thoracic and abdominal surgical procedures, orthopedic operations on the femoral cervix and the hip joint, operations on the pharynx and Ricrosurgical procedures. TEA is less effective during rapid operations since it takes 15 to 20-minutes for opioid peptides to be released and to induce analgesia. In patients with congenital or acquired tolerance to morphine-like analgesics, analgesia cannot be induced by transcranial electrostimulation.

Application of TEA during anesthesia is associated with residual analgesia early in the post-operative period, the duration of this residual analgesia being correlated with the duration of electrical stimulation during the operation and the intensity of this stimulation. TEA procedure may be used in an isolated manner for arresting the post-operation pain (Avrutski M. Ya. et al., 1983), which is particularly important after thoracic operations since TEA, unlike narcotic analgesics, does not inhibit respiration and cough reflex.

**TEA as a Means of Arresting Pain Syndrome.**

TEA can be used for arresting different pain syndrome as a physiotherapeutic procedure. It should be emphasized, as it has been stated above, that the onset of analgesic effect can be observed 10 to 15-minutes after the beginning of stimulation. TEA effect does not depend on the site of pain localization. As a rule, the greatest TEA effect can be achieved in those cases when pain afferentation is maintained at a relatively constant level. Consequently, TEA is comparatively less effective in renal colic, labor pain, short-term painful manipulations such as in dentistry and during passive joint exercise following joint operations.

The effect of TEA is similarly low in those cases when pain is associated with central mechanisms, that is, in thalamic pain, certain types of phantom-pain syndromes, trigeminitis with long-lasting history and, especially, in surgical treatment involving operations on the Gasserian ganglion. In all these cases, a central determinant pain focus seems to be formed, which supports the existence of pain syndrome regardless of the peripheral impulses (Kryzhanovski G. N., 1980).
Such difference in TEA efficacy between the pains of peripheral and central genesis connected with the fact that transcranial electrostimulation of the suprasegmental antinociceptive structures; a segmental “gate mechanism” of pain flow regulation is triggered due to the existence of descending pathways (Malzac, Wall, 1965). This hypothesis is supported by the fact that beta-endorphin concentration in the posterior horns of the animal spinal cord is significantly increased during TEA, which can modulate the pain impulse conduction (Airapetov L.P. et al., 1985).

During and after the TEA procedure, certain EEG parameters may be changed, showing the correlation with the sedative and analgesic effects. It was demonstrated that during TEA the amplitude of certain components of the induced acoustic potential became reduced (Shloznikov B. I., 1985), whereas after TEA θ waves were less pronounced on the EEG and there was a significant decrease in the amplitude of slow ξ and τ waves with a period of 2-4 to 20-s, these waves being especially marked in pain syndrome (Ilyukhina V. A., Lomarev M. P., 1987). At the same time, notwithstanding the fact that the impulse current of relatively large amplitude is used for the stimulation, no signs of the emerging epileptiform [resembling epilepsy] activity can be observed on EEG. On the contrary, if present, it may disappear following repeated TEA sessions.

The effect of a single TEA procedure is followed by a long-lasting analgesic after-effect, which is characteristic of the stimulation with combined rectangular impulses and direct current. The after-effect following a thirty-minute procedure may persist for 2 to 24-hr and increase in strength with each next session. When Limoge's currents are applied, the after-effect is usually short. However the stimulation with these currents itself may be continued for many hours since, in this case the patient's unpleasant feelings are minimized.

It is important to stress that, despite the opioid nature of TEA, patients do not develop any addiction to this procedure, although some of them speak of becoming high-spirited, relaxed or “getting high” following the TEA session. It is understood that the degree of analgesia depends not only on the selectivity of electrical stimulation of the antinociceptive system but also on the potential of this system in the individual patient. It can be not infrequently observed that in patients with long-lasting severe pain syndrome the efficacy of the second TEA procedure tends to be somewhat reduced as compared to that of the first one, carried out 12 to 24-hr earlier. The longer the interval, the greater the effect of each subsequent procedure.

The list of pain syndromes that could be successfully treated with TEA is large. In the first place, the pain syndromes that accompany neurological diseases should be mentioned. These syndromes may be divided into two groups as follows: those with pain at the sites of cerebral or spinal innervation [process of innervating].

In the first group, the beneficial effect of TEA was observed in neuralgias of different types associated mainly with neurovascular dystonia (Zabolotnykh V. A. et al., 1986) and migraine attacks (Akimov G. A., Volkov A. K., 1987). In the latter case, the beneficial effect can be objectivized [objectified] by rheoencephalography and the decrease in the level of skin thermo-asymmetry. At the same time, the effect of TEA is less pronounced in the patients with headache associated with verified arachnoiditis.
One special aspect of TEA application for combating headache is represented by analgesia during pneumoencephalography and pneumomyelography. The greatest effect can be achieved in that case when air is first introduced when the TEA procedure has already begun. In this case not only the headache can be reduced but also there is also significant diminution of the intensity of characteristic autonomic events such as nausea and vomiting which usually accompany the PEG procedure (Sorokoumov V. A. et al., 1984). When TEA is used, most patients will regain their activities on the second day following the procedure.

TEA was found to be highly effective both during the procedure itself and in terms of the prolongation of remission periods in patients with trigeminitis, especially in those with the history of trigeminitis not longer than 3 to 5-yr. Marked analgesic effect can be also observed in patients with severe pain following eye injury or operations affecting the ciliary body. At the same time this effect was less pronounced in patients with pain associated with terminal glaucoma (Kasimova M. D. et al., 1987).

The second group of pain syndromes is formed mainly by different spondylogenous radicular and autonomic pains as well as by pains associated with diseases or injuries of the limb nerves. As a rule, the effect of single TES procedures and the entire course of treatment is more pronounced when used during the acute period of the disease or at the moments of aggravation of the disorder. This effect leads to a rapid weakening of tension symptoms and the antalgic posture as well as to an increase in the scope of active motions, (Gretsov S. I. et al., 1987). Such properties of TEA together with the technical simplicity and safety of this procedure make TEA readily available for application to the ambulant treatment of patients. Under ambulant conditions, following the relief of acute pain syndrome, residual symptoms may be eliminated using different kinds of reflex therapy (Krasyukov A. V., 1987).

However, in the presence of gross changes in the vertebral column such as disc sequestration, despite the efficacy of isolated TEA sessions, no long-lasting analgesic after-effect can be achieved since the enlargement of the scope of motion during analgesia usually leads to the irritation of the radices and the outburst of pain impulses, which becomes strong enough to break through the slightly closed “gate mechanism”.

A certain efficacy of TEA was observed in patients with pain of visceral genesis. In this connection, the application of TEA for the treatment of patients with coronary heart disease accompanied by moderate pain syndrome should be mentioned (Belokrinitski V. I., Predelina Ye. A., 1986, Kukuy L. M. et al., 1987). It should be remembered in this case that TEA effect appears after a certain time interval and cannot be used for immediate elimination of anginal attack. However, the course of treatment may result in reduced attack intensity and frequency.

TEA was effective in the treatment pain accompanying gastric and duodenal ulcerative disease (Anisimov V. Ye., Rupasova T. N., 1985; Zilber Tu. D. et al., 1987).
Thus, the effect of TEA is universal in its character, which reflects the mechanism underlying analgesia, that is, the activation of the patient’s antinociceptive system. Though many thousands of TEA procedures, alone or in a combination with anesthesia were carried out, no significant side effects could be revealed. It is probably in this connection that any clear contraindications for the application of TEA have not yet been determined with accuracy.

**Non-Analgesic Effects of Transcranial Electrostimulation**

A brief survey of the effects that accompany the TEA procedure but are not associated with analgesia will be given below.

As it has been already stated, TEA can be successfully used for the treatment of headache that accompanies vegetovascular dystonia, for instance, of diencephalic origin. TEA was observed not only to eliminate pain but also to normalize the systemic hemodynamics, as it lowered the high and raised the low arterial blood pressure or reduced the amplitude of arterial blood pressure fluctuation (Zabolotnykh I. I. et al., 1987). The normalizing effect of TEA was demonstrated also regarding the unstable arterial hypertension (Gembitski Ye. V. et al., 1986). Probably the stabilizing influence of TEA on the hemodynamics is based, as it was demonstrated in experiments, on the ability of transcranial electrostimulation to affect the central links of vasomotor reflexes and directly the vasomotor center (Katsnelson Ya. S., 1985; Lebedev V. P. et al., 1986). Characteristically, such influence can be achieved only using the analgesic regimen of electrical stimulation and, like analgesia itself, is of opioid nature since it can be removed by naloxone.

Opioid peptide release into the blood during TEA may accelerate the regeneration processes. Such effect of TEA has been recently demonstrated in animal experiments (Ilyinski O. G. et al., 1987) and is now being supported by clinical observations. In any case, the accelerating influence on the reparation plays, no doubt an important role in the curative effect of TEA on yet been determined on patients with ulcerative disease when a significant acceleration of healing of the ulcerative defect can be observed even in the absence of pain syndrome. It cannot be excluded that the stimulation of reparative effect is important for the therapeutic action of TEA in patients with primary deforming arthritis (Zabolotnykh I. I. et al., 1987) and neurodermitis. There is no doubt that in these two last cases the analgesic effect is also of certain importance, the more so that itch may be regarded to be analogous to pain.

TEA-induced stimulation of the opioid mechanism begins to find its application as an effective means for arresting the alcoholic abstinence syndrome (Grinenko A. Ya. et al., 1986; Terebilina N. N., 1986). In this case the deviation from the analgesic regimen also results in the diminution of the therapeutic effect. The possibility to stimulate the opioid mechanism indicates that TEA might be promising for the treatment of opioid withdrawal syndrome. First results of the observation on patients with moderate drug consumption and relatively mild abstinence syndrome instill some hope. However, it should be remembered that long-lasting consumption of high doses of morphine like drugs may cause the exhaustion of endogenous opioid reserve (Gromov L. A. et al., 1985) so that the TEA procedure would result only in certain side effects.
While summarizing the data on the effects of TEA at an experimentally substantiated regimen, it should be noted that nowadays TEA is a promising, simple and safe method of combating pain. Further research should be directed towards the selection of pharmacological agents that could potentiate analgesia, producing no side effects characteristic of narcotic analgesics.

*Studies continue on page 127*
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PART I -- THEORETICAL BASIS FOR
A NEW METHOD OF TRANSCRANIAL ANALGESIA

CONTENTS
Ignatoy Yu. D. and Zaitsev A. A. Neuropharmacological aspects of the brain antinociceptive systems and stimulation analgesia ...............................................................129
Leosko V. A., Shiemis G. I., and Baranovsky A. L. The main electrical parameters and instrumentation for transcranial electroanalgesia ........................................131
Lebedev V. P., Katsnelson Ya. S., and Savchenko A. B. Experimental evaluation of analgesic effectiveness of several electroanalgesia regimens and the selection of optimal electrostimulation parameters .........................133
Kovalyov M. G. A comparative experimental study of the analgesic effects produced by a new transcranial electrostimulation method and by Limoge’s method....135
Lebedev V. P., Airapetov L. N., Katsnelson Ya. S., Savchenko A. B., and Petrayevskaya N. V. Activation of the brain antinociceptive system during transcranial electroanalgesia and the role of opioid and other mediator mechanisms in this effect ........................................................................137
Airapetov L. N., Glushchenko T. S., Taranova N. P., and Sinitsyn L. N. Topography of endogenous opioid peptide-binding zones in the brain.........................139
Medvedev 0. S., Fan A. B., Dughin S. F., Martynova Ve. R., and Glukhovtsev Ye. V. Experimental study of the effects of transcranial analgesia on systemic and regional hemodynamic parameters ........................................141
Fan A. B. and Krasuykov A. V. Experimental study of the effects produced by transcranial electroanalgesia on certain mechanisms of blood-flow regulation ..........143
Levtov V. A. and Shuvayeva V. N. Influence of transcranial electroanalgesia on blood rheology ........................................................................................................145
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NUMEROUS studies have demonstrated that electrostimulation of different brain structures, such as the central gray matter (CGM), the limbic structures, the hypothalamus, and others, will cause a marked analgesic effect characterized by the elevation of pain threshold level and checking of highly-integrated pain manifestations. These data provide a basis for recognition of the existence of a specific homeostatic mechanism, which possesses low tonic activity but acts under condition of aversive stimulation.

Experiments performed at our laboratory with wakeful cats have shown that analgesia caused by the mid-brain CGM stimulation may be accompanied by simultaneous inhibition of hemodynamic manifestations of nociceptive response. Marked parallelism between the dynamics of checking the behavioral responses, changes in arterial blood pressure and tachycardia, and direct relationship between analgesia and the intensity of central stimulation were revealed. It is, however, evident that the descending pain-modulating systems differ in their functions. In most cases, checking of multimodal [multi-genesis] pain manifestations during the CGM stimulation was accompanied by changes in spontaneous animal behavior and the development of arterial hypertension. It cannot be excluded that this is justifiable in regard to biological expediency since a close relationship between the homeostatic mechanisms of pain-perception regulation and the hemodynamics has been revealed, in particular, checking the emotional and behavioral responses in association with the activation of high-pressure baroreceptors. It is important to stress that peculiarities of action of the brain “antinociceptive systems” determine, to a great extent, the inter-individual differences in animal pain reactivity.

The neurochemical mechanisms of stimulation analgesia were analyzed in regard to up-to-date knowledge concerning the fundamental role of opioid and adrenergic [of or like epinephrine] systems in the regulation of pain responsiveness and hemodynamics respectively. It has been determined that the adrenergic mechanisms may be of some importance for the formation of emotion and autonomic function-correcting effects triggered by the CGM stimulation. Experiments with local injections of adreno-positive agents (clofeline, L-DOPA) and agents for pharmacological analysis (selective post and presynaptic adrenoreceptor antagonists, 6-hydroxy dopamine, etc.) indicated an important role of segment-level vasomotor mechanisms in the realization of the stimulation analgesia effects.
Comparative analysis of the data obtained during the systemic narcotic analgesics administration and microinjections of mu-, delta-, and kappa-opiate receptor agonists as well as of naloxone demonstrated the receptor mechanisms of the descending opioidergic regulation of emotional and behavioral as well as hemodynamical nociceptive responses and the possible potentiating interaction between the opioidergic and adrenergic processes of circulation regulation in pain.

The role of the brain analgesic systems in the formation of analgesic effect during acupuncture and transcranial electroanalgesia are discussed.

*Studies continued on the next page*
THE MAIN ELECTRICAL PARAMETERS AND INSTRUMENTATION FOR TRANSCRANIAL ELECTROANALGESIA

V. A. Leosko, G. I. Shlemis, and A. L. Baranovsky,
All-Union Scientific Research Institute of Pulmonology,
USSR Ministry of Public Health, Leningrad

Application of electric current for achieving analgesia was traditionally associated with various types of electrostimulation and instrumentation design. Investigators' attention was attracted not only to the variation of the parameters characterizing the stimulus strength and duration but also to the search for optimal stimulus shape.

Initially, while studying transcranial electroanalgesia (TEA), the constant electrical parameters were used. With the development of electronic technology, a tendency appeared towards electrical parameter variation within a wide range. At present, much attention is again paid to the application of stable and constant stimulation parameters for the treatment of different individuals.

Traditionally, the following types of electrical stimuli were mainly used:

1) Continuous impulse stimulation;
2) Sinusoidal current;
3) Interferential current;
4) Combination of continuous impulse stimulation with additional galvanic component varied within a narrow range; and
5) Combination of continuous impulse stimuli or packs of high-frequency impulses with additional galvanic component varied within a sufficiently extensive range.

Stable commercial production of instrumentation for TEA is restricted in this country [USSR] to the models such as Electrosleep and Electronarcon-1.

These apparatus as well as EA-12-01, LENAR, and PELANA models which became available more recently and all resemble, to a significant extent, the former ones represent, in fact, one and the same class of apparatus which provide the stimulation with continuous impulse stimuli combined with additional galvanic component varying within a narrow range.

The fact that apparatus such as Electrosleep are of only limited use for TEA is due to the superocular [above the orbit of the eye] positioning of electrodes with this model, which imposes certain restrictions on the variation range of impulse strength.
Frontal and occipital electrode positioning with Electronarcon-1 and its analogues allowed to employ the greater value of impulse stimuli and galvanic component. Recommendations exist for the use of stimulation provided by Electronarcon-1 and LENAR during anesthesia. However, the analgesic effect is only slightly pronounced, which requires to combine this stimulation with relatively wide range of pharmacological agents. Moreover, the danger of burn under the electrodes makes it necessary to undertake a complex of preventive measures in the course of prolonged surgical intervention.

At present, an Anesthelec apparatus [Limoge’s apparatus] has been designed in France, which provides the stimulation with packs of bipolar high-frequency impulses of fixed frequency. The absence of additional galvanic component and the specific properties of stimuli thus obtained allow to reduce unpleasant sensations under the electrodes and to exclude burns in patients.

In this country, the following models are now at different stages of their development: Skat, BILENAR, apparatus which is being developed at the USSR Academy of Medical Sciences, and apparatus for TEA discussed at this Conference (V. P. Lebedev et al.).

Skat apparatus action is based on the formation of stimuli closely to interference principle, i.e., short impulses are delivered in a defined sequence via the electrodes placed around the head. In its authors’ opinion (V. I. Sachkov et al.), these short impulses are summarized at the level of the brain tissue without producing any significant local effect.

With BILENAR apparatus (E. M. Kasrubit), an attempt is made of isolated stimulation of either the left or the right hemisphere due to stimulation with a combination of electrical parameters similar to those employed with PELANA-01 apparatus.

An apparatus which is being developed after the design proposed by the Institute of Surgery (M. I. Kuzin et al.) is, to a certain extent, an analogue to the Anesthelec apparatus; however, due to its action via two stimulation channels, it provides the possibility to expand this stimulation to a greater portion of the brain tissue.

With an apparatus which is being developed after the design proposed by V. P. Lebedev et al., a combination of continuous impulse stimuli of fixed frequency and duration with a galvanic component varied within a sufficiently wide range.

As could be judged by the previously published data and the proceedings of this Conference, the latter two types of apparatus are clinically the most effective ones, these apparatus possessing several common output characteristics, i.e., the stimulation fixed frequency value and the duration of high-frequency impulse packs and rectangular impulses. In these authors’ opinion, analgesia is achieved with these apparatus due to the stimulation of the brain endorphin system. Comparative analysis of the intensity of this influence could allow [us] to evaluate the effectiveness of these apparatus and define the indications for their rational application.
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART I -- THEORETICAL BASIS FOR A NEW METHOD OF TRANSCRANIAL ANALGESIA

EXPERIMENTAL EVALUATION OF ANALGESIC EFFECTIVENESS OF SEVERAL ELECTROANALGESIA REGIMENS AND THE SELECTION OF OPTIMAL ELECTROSTIMULATION PARAMETERS

V. P. Lebedev, Ya. S. Katsnelson, A. B. Savchenko
I. P. Pavlov Institute of Physiology of the USSR Acad. Sci., Leningrad

First attempts to achieve an analgesic or, to be precise, an anesthetic effect with the transcranial brain stimulation had been undertaken about one hundred years ago. Since that time, such attempts had been repeated in many countries but not until recently could a reproducible analgesic effect be achieved. This seems to be due to the fact that, in experimental studies quantitative methods were only rarely used for evaluation of the analgesic effect.

In a series of experiments utilizing various animal species, we evaluated the intensity of analgesia during transcranial electrostimulation (TLS). For this purpose, quantitative methods were used which are usually employed for estimation of the analgesic effect produced by pharmacological agents.

At first, preliminary evaluation of analgesic effects produced by a variety of stimulation regimens achievable with the use of different commercial homemade apparatus for electroanalgesia (EA-30-1, EA-12-01, and LENAR). Rectangular impulse frequency and duration were determined according to nonius indices of corresponding regulators, whereas the current amplitude was read from measuring devices of apparatus. In a certain part of experiments, more accurate methods were used for parameter measuring.

Stimuli were delivered via three electrodes, one of which a cathode, being placed at the forehead and the remaining two electrodes (anodes) being placed behind the ears. Effects produced with different impulse frequencies were tested, i.e., those produced by stimulation at following frequency ranges; from 50-Hz to 100-Hz with 10-Hz intervals; from 100-Hz to 3-kHz with 250-Hz intervals; and with the frequencies of 10 kHz, 25-kHz, and 50-kHz. With the frequencies ranging from 50 to 500-Hz, impulse duration was 0.1 to 1-ms; with the frequencies of over 500 Hz, the maximal impulse duration did not exceed 0.5 of the corresponding periods. Additionally, TES was also carried out with the periodical high-frequency impulse series (impulse frequencies of 10-kHz and 100-kHz), this periodicity being 100-Hz in frequency with impulse series duration of 1 to 5-ms.

No primary analgesic effect could be observed in any of the cases despite the increasing of current value up to the cramp threshold.

The observable primary analgesic effect (AL) occurred only when rectangular impulses of maximal duration at frequencies of 50 to 750-Hz were delivered in a combination with direct current, the AL being more pronounced at frequencies of 60 to 90-Hz.
At the second stage of our investigation, a thorough screening study of various combinations of rectangular impulses 60 to 90-Hz in frequency was performed, impulse duration ranging from one to 5 ms. Different direct current/average impulse current ratios were examined. It has been established that the maximal analgesic effect with the minimal current value occurred in rabbits at impulse frequency of 77 to 78-Hz, impulse duration of 3 to 4-ma, and direct current/average impulse current ratio of 2:1 to 5:1. These findings allow [us] to conclude AL could be achieved with the use of highly critical TES parameters.

At the third stage, this conclusion was verified by metrologically correct TES parameter measuring. It was taken into account that any change in an isolated TES parameter would inevitably cause changes in other parameters and parameter ratios. The findings of this experimental series provided a strong support for our previous conclusion that the AL could be induced only by stimulation with rectangular impulses of critical frequency and duration parameters and of critical direct current/average impulse current ratios.

Data obtained during the fourth experimental stage have demonstrated that pronounced analgesic effect with minimal local irritating effect could be achieved only when replacing rectangular impulses by periodical series of high-frequency impulses 10-kHz in frequency and with 1.6 to 2.5-ms intervals delivered together with previously switched-on direct current at the same parameter range.

Clinical studies performed in healthy volunteers, patients with chronic pain syndromes, and patients undergoing anesthesia with the use of different methods of measuring the pain response intensity confirmed the effectiveness of chosen TES parameters and parameter criticity.
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART I -- THEORETICAL BASIS FOR A NEW METHOD OF TRANSCRANIAL ANALGESIA

A COMPARATIVE EXPERIMENTAL STUDY
OF THE ANALGESIC EFFECTS
PRODUCED BY A NEW TRANSCRANIAL
ELECTROSTIMULATION METHOD
AND BY LIMOGE’S METHOD

M. G. Kovalyov, All-Union Scientific Research Institute of Pulmonology
USSR Ministry of Public Health, Leningrad

Transcranial electrostimulation (TES) with impulse current parameters proposed by Limoge (1975) has recently become available in France and, subsequently, in our country. According to Limoge’s method, TES is performed with the application of bipolar high-frequency impulse packs (frequency of 180-kHz) delivered at a frequency of 77-Hz with periodical switching-over to 83 and 100-Hz frequencies and duration of 3 to 4-ms.

The principal advantage of this method is associated with the fact that, due to the application of high-frequency impulses, unpleasant sensations at the sites of electrode positioning can be minimized, and, due to the bipolar impulse structure, the possibility of electrochemical burn occurrence can be excluded.

It seemed necessary to compare experimentally the intensity of analgesic effects (AE) produced by TES with Limoge’s currents as well as by TES with parameters proposed by V. P. Lebedev et al. (1964). Following characteristics are common for both of these regimens: similar fixed frequency and duration of impulse packs and rectangular impulses as well as the possible endorphin involvement in AE produced with both regimens of stimulation (Kuzin et al., 1984; Airapetov et al., 1985).

TES was performed in rabbits with the use of a modified EA-30-1 apparatus model (impulse current frequency of 77-Hz; impulse duration of 4-ms), average impulse current/direct current ratio being 1:2 (experimental animal group), and an experimental model of EA-300-1 apparatus producing Limoge’s currents (control). TES effectiveness was evaluated using the impulse summation method (Zakusov, 1940) while measuring the degree of arterial blood pressure pain response inhibition (pressor [causing an increase in blood pressure] and depressor responses secondary to stimulation of ischiatic [ischial] nerve and vagus [nerve] respectively) as well as the AE-linked inhibition of response to depressor nerve stimulation. Simultaneously, the influence of TES on rabbit respiratory rate was studied.

During TES with Limoge’s currents 300 mA in amplitude (the current values generally used for anesthesia in man), the number of impulses, which would cause the motor escape reaction increased gradually to reach a 218% value as compared with the initial value after 30-min of stimulation. In contrast, when performed according to the method proposed by V. P. Lebedev et al., TES caused an increase in the number of impulses required to induce motor response as early as immediately after switching-on of the current.
This increase was to 274% and 288% for impulse current amplitude values of 4 mA and 8 mA respectively. In the latter case, the total current value was three times less than that usually employed for electrostimulation during anesthesia in man (Katsnelson, 1985). Statistical analysis has shown that AE produced by TES with Limog’s currents the value of which was limited by EA-300-1 apparatus’ characteristics did not differ significantly from that achieved with the smallest of all examined direct current/average impulse current ratio values.

There was no enhancement of AE when periodical frequency substitution system intrinsic to EA-300-1 apparatus was being used. To the contrary, the AE level rather underwent undulating reduction.

During TES with maximal-value Limoge’s currents, a certain decrease in the intensity of arterial blood pressure pain pressor response could be observed. However, during TES with combined direct and impulse currents, the latter’s amplitude value being of 8 mA, such decrease in the response intensity was 2.1 times as large. Decreases in the intensity of depressor responses to the vagus and depressor nerve stimulation were respectively 2.1 and 2.3 times as large.

With both TES regimens, a certain decrease in animal respiratory rate could be registered, this decrease being less pronounced with the application of Limoge’s currents. The decrease in respiratory rate was becoming less marked with the course of TES.

These findings have demonstrated that, with given experimental regimens, the intensity of AL produced by Limoge’s currents is lower than that of AL produced by a combination of direct current with rectangular impulses, notwithstanding the fact that, in the latter case, much lower current values were used, both in their absolute meaning and in their relative expression as compared with those employed for anesthesia in man.
ACTIVATION OF THE BRAIN ANTINOCICEPTIVE SYSTEM DURING TRANSCRANIAL ELECTROANALGESIA AND THE ROLE OF OPIOID AND OTHER MEDIATOR MECHANISMS IN THIS EFFECT

V. P. Lebedev, L. N. Airapetov, Ya. S. Katsnelson, A. B. Savchenko, and N. V. Petryayevskaya,
I. P. Pavlov Institute of Physiology of the USSR Acad. Sci., Leningrad

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 sutural 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, serotonergic, 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 radioimmunoassay.
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.
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART I -- THEORETICAL BASIS FOR A NEW METHOD OF TRANSCRANIAL ANALGESIA

TOPOGRAPHY OF ENDOGENOUS OPIOID PEPTIDE-BINDING ZONES IN THE BRAIN

L. N. Airapetov, T. S. Glushchenko, N. P. Taranova, and L. N. Sinitsyn,
I. P. Pavlov Institute of Physiology of the USSR Acad. Sci., Leningrad

Previously, it has been shown that, during transcranial electroanalgesia, the brain opiate systems become activated (Airapetov et al., 1985; Lebedev, 1986). In this connection, it seems important to study the specific binding of endogenous opioids released during TEA to opiate receptors intrinsic to the different brain regions. Of particular interest are \( \mu_1 \)-isoreceptors to which analgesic, hemostabilizing, and some other effects of opiates have been ascribed (Ling et al., 1983; Pfeifer et al., 1983).

We studied the competitive binding in vivo of \( \mu_1 \)-receptor endogenous ligands to radio-labelled mu-agonist, \( \text{\textsuperscript{2-125}} \) morphine, in the brain of rats during TEA.

During TEA with application of electric current corresponding in its value with the anesthesiological level, \( \text{\textsuperscript{2-125}} \) I-morphine was released from its receptor binding sites. There were: a 71\( \pm \)5\% release in the dorsal sutural nucleus (DSN); an 80\( \pm \)2\% release in the periaqueductal gray matter (PGM); and an 85\( \pm \)3\% release in the dorsomedian hypothalamic nucleus (DHN). This correlated well with pharmacological data, which suggest the absence of additivity between the analgesic effects, produced by TEA and by such analgesics as phentanyl and morphine (Airapetov and Sinitsyn, 1986).

Comparative analysis of specific binding during TEA of diverse intensities revealed the saturating nature of relationships between the calculated endogenous opiate-binding levels and the current value. [In this contest value mean mA. The more mA then more intensive analgesic effect]. With analgesic-level current, there were: an 1.8-fold increase in opiate binding in the DSN; an 1.9 increase in the PGM; and an 1.6-fold increase in the DHN. With anesthesia-level current, the opiate-binding intensity was 3.4-times (DSN), 5.1-times (PGM), and 6.9-times as great (DHN) as that in control. Nonlinear regression equations, which describe the relationship between the percentage of endogenous opiate binding (B) and the TEA current strength (i) are as follows:

\[
\begin{align*}
B_{\text{DSN}} &= 43.57 - 36.04 \exp(-0.164 \ i) \quad (1) \\
B_{\text{PGM}} &= 60.64 - 52.12 \exp(-0.153 \ i) \quad (2) \\
B_{\text{DHN}} &= 355.35 - 340.47 \exp(-0.031 \ i) \quad (3)
\end{align*}
\]

The equations indicate that the slope of \( B/i \) relationship curve is the steepest one in the case of the DHN (3) and the slightest one in the case of the DSN (1). Evidently, there must be an optimal current value the exceeding of which will not exert any marked influence on endogenous opiate binding. It is noteworthy such optimum values differ from structure to structure.
Our findings confirm the absence of synergism between the effects of morphine and endogenous opiates released during TEA, which should be regarded as a contraindication for combined administration of narcotic analgesics and TEA in clinical practice. The saturating character of relationship between the endogenous opiate binding level and the intensity of TEA suggests that it would be impossible to enhance the analgesic effect of TEA when strength of the current exceeds certain optimal values used for analgesia during surgery.

Thus, the main consequence of TEA-induced changes in topography of opioid peptide release in the brain is the increase in opioid peptide contents in certain principal structural elements of the antinociceptive system. These data could be of use for understanding such TEA effects as the correction of nociceptive hemodynamic responses, the arresting of alcoholic abstinence syndrome, and the acceleration of lesion healing.

*Studies continued on next page*
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART I -- THEORETICAL BASIS FOR A NEW METHOD OF TRANSCRANIAL ANALGESIA

EXPERIMENTAL STUDY OF THE EFFECTS OF TRANSCRANIAL ANALGESIA ON SYSTEMIC AND REGIONAL HOMODYNAMIC PARAMETERS

O. S. Medvedev, A. B. Fan, S. F. Dughin, Ye. R. Martynova, and Ye. V. Glukhovtsev,
Institute of Experimental Cardiology, All-Union Cardiological Center, Moscow

The present study was designed to examine in the course of animal experiments the effects produced by transcranial electrostimulation on cardiac function, and local blood flow. The latter seemed to be of particular importance since it had not been clear thus far whether this method of analgesia produced any reduction in the blood flow through the vitals.

In our experiments, nembutal-narcotized rabbits were used under administration of artificial ventilation of the lungs and myorelaxants. The effects of TEA were studied at different current levels. TEA-I was performed using the current strength, which is usually employed for anesthesia. In TEA-II, the current level was by 1/3 higher, suggesting that, in this case, possible adverse side effects of TEA could be revealed.

TEA-I did not cause any significant changes in arterial blood pressure (ABP) or cardiac rate (CR). With TEA-II, ABP increased from 107.6±15.9-mm/Hg to 142.0±5.6-mm/Hg. Hypertension could be abolished by means of ganglioblocker injection but not by naloxone injection. Cardiac rate diminished from 323.8±11.4 to 277.6±14.7 beats per minute. Both TEA regimens caused no alterations in the general structure of ECG (lead II) as well as in PQ or QT intervals, which suggests that there were no change in atrilventricular or intraventricular conduction. Bradycardia disappeared after bilateral vagotomy, atropin or naloxone injection.

Cardiac output (CO), general peripheral resistance (GPR), and local blood flow were measured as follows. Plastic micro-spheres, 1-mm in diameter, labeled with $^{141}$Ce, $^{46}$Sc, and $^{95}$Nb (NEN, USA) were introduced through a catheter into the left ventricle of each animal before and during TEA-I and TEA-II. Simultaneously, the blood was drawn from the femoral artery at a rate of 3-ml blood/min. Amount of microspheres in blood specimens thus obtained was measured with the use of gamma-counter 1282 Compu-Gamma (LKB) designed for separation of up to 5 isotope types. CO and regional blood flow were calculated using the standard formula with a computer model 3015 (Labtam) (Supercals -2 program).

Copy and table continued...
TEA-I and TEA-II did not cause any significant changes in CO or GPR. The data concerning regional hemodynamic parameters are summarized in the table:

### Influence of TEA on regional blood flow

<table>
<thead>
<tr>
<th>Organs and tissues</th>
<th>Baseline</th>
<th>TEA-I</th>
<th>TEA-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>0.02±0.00</td>
<td>0.05±0.01</td>
<td>0.03±0.00</td>
</tr>
<tr>
<td>Muscles</td>
<td>0.05±0.01</td>
<td>0.05±0.02</td>
<td>0.03±0.01</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.38±0.05</td>
<td>0.47±0.11</td>
<td>0.30±0.06</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.46±0.04</td>
<td>0.51±0.14</td>
<td>0.37±0.11</td>
</tr>
<tr>
<td>Intestine</td>
<td>0.53±0.10</td>
<td>0.73±0.15</td>
<td>0.50±0.12</td>
</tr>
<tr>
<td>Spleen</td>
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<td>0.79±0.09</td>
<td>1.98±0.47</td>
</tr>
<tr>
<td>Liver</td>
<td>0.10±0.04</td>
<td>0.09±0.02</td>
<td>0.11±0.04</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.20±0.50</td>
<td>4.66±1.45</td>
<td>3.25±0.63</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>1.30±0.09</td>
<td>1.89±0.40</td>
<td>1.54±0.14</td>
</tr>
<tr>
<td>Lungs</td>
<td>1.47±0.47</td>
<td>1.27±0.37</td>
<td>1.39±0.25</td>
</tr>
<tr>
<td>Heart</td>
<td>3.32±0.83</td>
<td>2.76±0.34</td>
<td>2.89±0.82</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>0.21±0.06</td>
<td>0.43±0.08*</td>
<td>0.42±0.06*</td>
</tr>
</tbody>
</table>

* p <0.05

As it is shown in the table, significant changes in regional blood flow could be observed only in the cerebral cortex, with both TEA regimens. TEA-II caused a 16% increase in the cerebral fraction of GO. It seems probable that the increase in cerebral blood flow was due to the local electric current’s effect.

Our findings lead to a conclusion that TEA will not induce any disturbances in the systemic or regional hemodynamics. The mechanism underlying hypertension induced by TEA-II is, no doubt of central origin but, contrary to most other TEA effects, this mechanism is not associated with the brain opiate system. This issue requires further investigation.
EXPERIMENTAL STUDY OF THE EFFECTS PRODUCED BY TRANSCRANIAL ELECTROANALGESIA ON CERTAIN REFLEX MECHANISMS OF BLOOD-FLOW REGULATION

A. B. Fan, A. V. Krasyukov, All-Union Scientific Research Institute of Pulmonology, USSR Ministry of Public Health, Leningrad

It has been noted that, when transcranial electroanalgesia (TEA) performed according to a method proposed by V. P. Lebedev et al. (1984) is added to the complex of anesthesiological methods, patients’ hemodynamic parameters remain unchanged despite marked nociceptive afferentation from the operational wound during traumatic stages of surgical intervention, blood loss, and other factors. Since narcotic analgesics are not administered in such cases and the doses of general anesthetics and other drugs can be significantly reduced, it could be suggested that it is TEA that stabilizes patient’s hemodynamics. In this connection, it was of interest to study the influence of TEA on pain and non-pain reflexes and systemic hemodynamics.

Experiments performed in superficially narcotized rabbits have shown that arterial blood pressure pressor reflexes (PR) caused by stimulation of A- and C-afferent of the ischiatic nerve were significantly reduced even when electric current of threshold level was used for TEA, this effect being observable only with those impulse current parameters which were optimal for achieving the analgesic effect. With the increase in the current value up to the anesthesia level, an almost complete inhibition of PR could be observed, whereas arterial blood pressure remained unchanged or was elevated.

Analysis of PR-inhibiting mechanisms was carried out using narcotized cats. Electrophysiological examination has demonstrated that, during TEA, inhibition of a delayed component of somatosympathetic reflexes occurred. This component is closed at the vasomotor level of the medullar ventrolateral surface (MVLS) and is responsible for the PR formation in narcotized animals (Lebedev et al., 1984). Inhibition of long-latent responses in white connective branchlets to the direct MVLS stimulation could be observed during TEA. Additionally, experiments performed in rabbits with previously induced vertebral arterial occlusion have demonstrated that a potent pressor response to cerebral ischemia caused by carotid clamping, the formation of which involves participation of MVLS structures (Dampney, Moon, 1980), underwent a 50% decrease during TEA. These data suggest that inhibition of PR to pain stimulation of the somatic afferent occurs due to the direct or indirect TEA influence on the bulbar level at which PR are closed.

Other reflex pressor and depressor effects on arterial blood pressure, which are closed at the bulbar level produced via baroreceptors (in response to the clamping of carotids and the depressor nerve stimulation) or by stimulation of the vagus (without depressor stimulation) were also reduced during TEA. The maximal effect could be achieved at an impulse current frequency optimal for analgesia. However, unlike the induced reflexes caused by stimulation of the ischiatic nerve, endogenous reflexes conducted from baroreceptors and reflexes induced by stimulation of the vagus could be inhibited during TEA at anesthesia current level only by 50 to 55%.
Coincidence of optimal electrical regimens between analgesia and hemodynamic-reflex blocking as well as the suppression of analgesia and of change in all the mentioned cardiovascular reflexes in response to the injection of naloxone, an opioid-receptor blocker, suggest the existence of common mechanisms underlying analgesia and hemodynamic stabilization during TEA.

Since it has been proved that TEA is associated with activation of the endorphin mechanisms in the brain stem, the above data leads to a conclusion that stabilization of hemodynamics could be also due to activation of the antinociceptive system.

Studies continued on next page
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART I -- THEORETICAL BASIS FOR A NEW METHOD OF TRANSCRANIAL ANALGESIA

INFLUENCE OF TRANSCRANIAL ELECTROANALGESIA ON BLOOD RHEOLOGY

V. A. Levtov and V. N. Shuvayeva,
I. P. Pavlov Institute of Physiology of the USSR Acad. Sci., Leningrad

Increase in blood viscosity and non-Newtonian properties will lead to an essential impairment of microcirculation and to considerable complications in numerous disorders (Levtov et al., 1982). Blood viscosity may become significantly increased in the areas of trauma pain and inadequate anesthesia during surgical intervention (Gelin, 1962; Van’kov, 1972; Dintenfass, 1976). A method of transcranial analgesia (TEA) (Lebedev et al., 1984), which is being increasingly employed in clinical practice, has not been thus far evaluated as to its effect on blood rheological properties.

Heparinized blood specimens were taken from rats divided into 4 groups. Following rheological parameters were measured: hematocrit (H, % v/v); total protein plasma concentration (Cp% w/v); red blood cell-aggregation time (ta, s); plasma viscosity (ηpl, mPa s) measured by means of rotation viscosimetry; breaking shear stress (τo, mPa) for blood at a standard H-40% (v/v); and differential external blood viscosity (η, mPa s). The latter parameter was expressed as a relationship between shear stress (τ, mPa) and shear rate (γ, s-1) at γ=(0.6/23.6)s-1. Group I included those animals, which underwent only this inevitable procedure and immobilization stress. Group II rats underwent TEA according to a method proposed by A. B. Savchenko, with strength of the current significantly exceeding the level, which is used for anesthesia. This allowed [us] to perform operations on the blood vessels without administration of any other anesthesia agents. Group III rats differed from group II rats in that they underwent an additional nociceptive stimulation during TEA. Group IV animals were treated the same way with the exception of TEA. The results are summarized in the table:

<table>
<thead>
<tr>
<th>Blood rheological parameters</th>
<th>Animal group I</th>
<th>Animal group II</th>
<th>Animal group III</th>
<th>Animal group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>55.0±1.3</td>
<td>46.4±0.4*</td>
<td>52.4±1.9</td>
<td>55.4±1.1</td>
</tr>
<tr>
<td>ηpl</td>
<td>1.74±0.04</td>
<td>1.50±0.03*</td>
<td>1.52±0.05*</td>
<td>1.70±0.01</td>
</tr>
<tr>
<td>Cp</td>
<td>8.86±0.18</td>
<td>7.20±0.20*</td>
<td>7.96±0.28*</td>
<td>8.60±0.20</td>
</tr>
<tr>
<td>ta</td>
<td>1.31±0.17</td>
<td>2.32±0.11*</td>
<td>2.36±0.45</td>
<td>1.36±0.10</td>
</tr>
<tr>
<td>τo</td>
<td>6.4±1.4</td>
<td>6.2±0.3</td>
<td>8.1±0.9</td>
<td>20.3±4.2*</td>
</tr>
<tr>
<td>η (0.6 s⁻¹)</td>
<td>31.7±3.7</td>
<td>29.9±2.4</td>
<td>30.8±1.9</td>
<td>62±10.4*</td>
</tr>
<tr>
<td>η (23.6 s⁻¹)</td>
<td>10.2±0.5</td>
<td>10.2±0.8</td>
<td>8.0±0.6*</td>
<td>10.3±0.9</td>
</tr>
</tbody>
</table>

* differing significantly from group I

Continued...
In group II rats, which underwent only TEA, lower hematocrit values were found (as compared with group I) and the signs of hemolysis could be observed. There was also a decrease in plasma viscosity and plasma protein contents, and red blood cell-aggregation time was shortened. In general, four of the 7 rheological parameters were reduced in this group as compared with group I. Thus, TEA does not at all deteriorate blood shear flow; TEA causes slight hemolysis, decrease in plasma viscosity and protein contents, and slowing-down of red blood cell aggregation. In group III animals which underwent nociceptive stimulation during TEA, plasma viscosity was significantly lower than that of group I animals and corresponds with that observed in group II animals. Similar correspondence was found for red blood cell-aggregation time. Protein concentration in group III rats was significantly lower than that of group I animals but it was greater than that observed in group II rats. Blood viscosity at \( \gamma=(3.8\pm23.6)\text{s}^{-1} \) was significantly reduced as compared with that in groups I and II. Group IV rats, which underwent nociceptive stimulation and were not protected by TEA had the worst rheological indices characterizing breaking shear stress and blood viscosity with all the shear rate values examined. Thus, it was determine that, in the absence of TEA, blood fluidity was impaired.

In conclusion, TEA will not induce undesirable changes in rheological properties of blood which could impair blood fluidity and it will prevent the development of such changes during nociceptive stimulation.
PART II -- APPLICATION OF A NEW METHOD OF TRANSCRANIAL ELECTROANALGESIA IN ANESTHESIOLOGY

CONTENTS


Vanevsky V. L. and Grinchenko S. A. Comparative study of the effectiveness of two electrostimulation methods for anesthesia during surgical operations .................. 153

Kvartovkin K. K., Goncharova Ye. S., and Baranovsky A. P. Transcranial electroanalgesia: A method of prevention of hypoxic CNS lesion in pediatric practice ........................................ 155


Bobrov Yu. F., Gamayunova V. B., Lazo V. V., Radin A. I., and Tamarin Ye. L. Electroanalgesia as a component of anesthesia during the operations for laryngeal tumors ...................................................... 159

Voitenko R. I., Kokin G. S., and Kapustin S. M. Transcranial electroanalgesia in patients with injured peripheral nerves .................................................................................. 161

Samoilov K. A., Kustov V. M., Zhuchkov S. L., and Zavaritski A. D. Transcranial electrostimulation analgesia in the orthopedic clinic ......................................................... 163

Vyskubova A. I. and Yuferov V. I. Experience with transcranial electroanalgesia as a component of anesthesiological support in patients with extra-pulmonary tuberculosis localization .............................................................................. 165

Zamyatnina N. M. Evaluation of a new method of electroanalgesia during orthopedic surgery in children ................................................................................................. 167

Lobzhanidze A. A. and Korneva Ye. A. Experience with the application of a new method of transcranial electroanalgesia under conditions of the trauma-tological department of a district hospital ............................................................. 169
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EVALUATION OF THE EFFECTIVENESS OF A NEW METHOD OF TRANSCRANIAL ELECTROANALGESIA FOR CLINICAL ANESTHESIOLOGY

Ya. S. Katsnelson, V. A. Leosko,
All-Union Scientific Research Institute of Pulmonology,
USSR Ministry of Public Health, Leningrad

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-operational 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.

*Studies continued on page 153*
COMPARATIVE STUDY OF THE EFFECTIVENESS OF TWO ELECTROSTIMULATION METHODS FOR ANESTHESIA DURING SURGICAL OPERATIONS

V. L. Vanevsky, S. A. Grinchenko, S. M. Kirov, State Postgraduate Medical Institute

The method of transcutaneous brain electrostimulation employed for anesthesiological support during surgical operations and, therefore, referred to as electroanesthesia (EA) was used in more than 500 cases, 310 of which were thoroughly analyzed. The results of comparative analysis of two electrostimulation methods used in this country are described below.

The first method of electrostimulation proposed by L. S. Persianinov et al. (1972) was performed with the use of a standard Electronarcon-1 apparatus with following electric parameters: frequency was 400 to 1000 Hz; impulse duration was 0.4 to 0.6 milliseconds; galvanic component measured from 0.5 to 0.8 mA; and average impulse current was 2.2 to 2.5 mA.

The second method of electrostimulation proposed by V. F. Lebedev et al. (1984) was carried out with the use of a modified Electronarcon-1 apparatus with output electric parameters as follows: frequency of 77 Hz; impulse duration of 3.5 ms; galvanic component of 8 to 10 mA; and average impulse current of 4 to 5 mA. The polarity of stimulation was switched-over at 10-min intervals.

Electrostimulation was combined with other methods and means of up-to-date anesthesiology, i.e., nitrous oxide, barbiturates, peridural [epidural] anesthesia, and others. Operations were performed under artificial pulmonary ventilation.

Clinical examination included the determination of central and peripheral circulatory indices, biochemical stress responses, and several indices of nonspecific resistance and adaptation abilities of the organism.

Our analysis revealed the significant differences between the two patient groups. Thus, with the first EA method, premature awakening and cramp-like episodes occurred not infrequently during the operation, while early in the postoperative period, psychiatric disorders could be observed in separate cases, which persisted from several hours to several days.

Cardiac output indices during lung operations with the application of the first method of EA tended to decrease, which was associated with the increase in peripheral vascular resistance. Reverse changes in these parameters could be observed when the second EA method was used, i.e., an increase in cardiac output was associated with the decrease in peripheral vascular resistance.
Application of the modified EA method allowed to diminish significantly the volume of required infusion therapy and hemotransfusions [blood transfusion] to 75.8% as compared with control group. High adaptively of the organism was confirmed by examination of pain intensity and degree of postoperative residual analgesia.

In general, the more beneficial clinical course, the absence of psychiatric disturbances during the postoperative period, insignificant influence on circulation indices, and some other advantages make the second method more preferable for clinical application.

Studies continued on the next page
TRANSCRANIAL ELECTROANALGESIA: A METHOD OF PREVENTION OF HYPOXIC CNS LESION IN PEDIATRIC PRACTICE

K. K. Kvartovkin, Ye. S. Goncharova, and A. P. Baranovsky, Medical Institute, Volgograd

Previous studies have shown the high effectiveness of a method of general electroanalgesia (GEA) (LEBEDEV et al., 1984).

A comparative study of the effectiveness of mixed fluothane/nitrous oxide/oxygen anesthesia and the method of GEA allowed to reveal significant advantages of GEA. This was particularly noticeable in the course of operations; which were associated with the loss of large amounts of blood (over 25-ml/kg body weight) and, subsequently, with hypoxia.

30-patients, aged from one to seven-years were examined. These patients underwent extensive orthopedic (15) and visceral (15) operations, which lasted not less than 2.5-hr. Before and during the operation parameters of acid-base balance, blood electrolyte spectrum, and blood-clotting system condition were measured. In addition, variation pulsometry was performed according to the method proposed by Bayevski.

Under conditions of fluothane anesthesia, the main homeostatic parameters in children varied within the normal range. Variation pulsometry demonstrated that, under fluothane anesthesia, the tension index (TI), which reflects the level of interrelations between the sympathetic and parasympathetic divisions of the autonomic nervous system steadily increased from 1,031.5±448.4 before the operation to 3,418.2±560.8 by the end of the operation, which correlated well (r=0.72) with the volume of blood loss.

Under conditions of GEA (20-observations), the blood homeostatic parameters during the operation and analgesia were also stable, however, the TI value steadily decreased from 1,099.8±153.4 to 847±135.2 and, moreover, there was a tendency towards a correlation between the volume of blood loss and the decrease in TI. The data thus obtained suggested that, under conditions of GEA, the CNS resistance to hypoxic lesion would possibly increase.

In order to verify this hypothesis, we added the method of GEA to the treatment complex administered to 12-children with obstructive respiratory insufficiency associated with complicated acute respiratory viral infections. Current loading via the electrodes was 30 to 40% to the level used for general anesthesia and did not exceed that of individual tolerance. GEA sessions lasted for 2 to 3-hr with similar intervals between them. There was a marked decrease in duration of the clinical period of toxico-hypoxic CNS lesion from 49.7±11.2 to 21.3±5-hr; patients’ condition in regard to the underlying disease ameliorated and purulent and septic complications occurred less frequently.
Formalization of TI in this patient group can also be considered as an objective criterion of GEA efficiency in the complex intensive therapy for the treatment of toxico-hypoxic lesions of the CNS. In conclusion, the method of GEA could be recommended for application as a means for protection and prevention in toxico-hypoxic lesions of the CNS in young children.

*Studies continued on the next page*
DIMINUTION OF VASCULAR BED’S CAPACITY IN THE PULMONARY CIRCULATION DUE TO RESECTIONS OF THE LUNG RENDERS THE PULMONARY CAPILLARY BED MORE RESPONSIVE TO THE EFFECTS PRODUCED BY VARIOUS FACTORS, WHICH ARE ABLE TO ALTERANT [TO CHANGE] THE FLUID METABOLISM IN PULMONARY TISSUES. SUCH FACTORS INCLUDE GENERAL ANESTHESIA AND IN-FUSION AND TRANSFUSION THERAPY, WHICH ARE USED DURING THE OPERATIVE INTERVENTION.

Using the methods of pulmonary tissue fluid volume determination designed at our Institute, we obtained the data, which provide an evidence that, with usual methods of anesthesia during thoracic surgery, significant changes in pulmonary circulation and intercapillary fluid metabolism occurred in patients. These changes were the most pronounced in patients with the history of pulmonectomy [removal of part or all of a lung’s tissue].

The pulmonary circulation and pulmonary tissue fluid metabolism were studied in 30-patients who had their lungs resected in 10-of these cases pulmonectomy was performed) under condition of transcranial electroanalgesia (TEA). The control group included 25-patients for whom thoracic operations were performed under general fluothane anesthesia.

After the initiation of narcosis as well as after the thoracotomy and during the operation on the pulmonary root, lung tissue hypoperfusion was found to be less pronounced under TEA than it was under fluothane. The cardiac index value was significantly greater. The increase in pressure in the left atrium, as could be judged by pulmonary occlusion pressure, was significantly less pronounced both during the operation on the pulmonary root and at the moment of pulmonary artery ligature. Increase in intravascular pressure in the pulmonary circulation in response to the diminution of pulmonary vascular bed was significantly less pronounced under TEA despite the relatively greater cardiac index. With relatively more stable systemic pulmonary hemodynamic parameter level and similar volume of blood loss of about 700-ml, the compensation volume under TEA was 258% related to the volume of blood loss, whereas under fluothane it was 359%. By the end of the operative intervention, in both patient groups an increase in the extravascular fluid volume had been observed in the lungs, however, in [the] fluothane group it was 277%, whereas in TEA group it was only 211%.
Thus, during the operations associated with the diminution of the pulmonary vascular bed’s capacity, TEA, acting both directly and indirectly via reduction of supporting infusion and transfusion therapy, will allow, to a much greater extent as compared with fluothane, to prevent the development of surgical intervention’s sequelae. The application of less voluminous infusions during the operative intervention stage is able to prevent the disfunctions associated with hypertransfusion in patients with diminished pulmonary vascular capacity reserve.

This allows [us] to consider TEA as a method of choice for patients at high risk of pulmonary edema.

*Studies continued on the next page*
ELECTROANALGESIA AS A COMPONENT OF ANESTHESIA DURING THE OPERATIONS FOR LARYNGEAL TUMORS

Yu. F. Bobrov, V. B. Gamayunova, V. V. Lazo, A. I. Radin, and Ye. L. Tamarin,
City Hospital no. 8 (Oncological Hospital), Leningrad

Operations for laryngeal tumors belong to the most trauma ones since they are performed in the close vicinity to reflexogenic zones of carotid bifurcation and associated partial vagotomy.

Comparative evaluation of anesthesia with the use of transcranial electroanalgesia (TEA) and neuroleptanalgesia (NLA) was performed which was based on the analysis of secretion of the “stress” hormones such as somatotropic hormone (STH), prolactin, cortizole, and adrenocorticotropic hormone (ACTH) measured by radioimmunoassay. Hormonal changes due to the surgical aggression could lead, in the case of inadequate anesthesia, to the metabolic changes causing the increase in postoperative complications, immunodepression, and further development of the tumor.

45-patients, 57±4.8-yr in age, were examined. In group I including 28-patients anesthesia was performed with the application of TEA, while in group II including 17-patients it was performed with the use of NLA. Mean operation time was 2.5-hr.

In group I, premedication included seduxene (0.1 to 0.2-mg/kg), atropin (0.1 to 0.2-mg/kg), and droperidol (0.08 to 0.15-mg/kg). In group II patients received additionally phentanyl (1.8 to 3-mg/kg) and dipidolor (0.2 to 0.4-mg/kg). Artificial ventilation of the lungs in both groups was performed with the use of nitrous oxide mixed with oxygen at a ratio of 3:1 against the background curarization with tubarin the expenditure of which did not differ significantly between two groups. For the support of anesthesia, TEA was used in the first group at a regimen proposed by V. P. Lebedev et al. (1984) in combination with fractional introduction of droperidol (0.14±0.04-mg/kg per hour). In group II, support of anesthesia was carried out by means of fractional introduction of droperidol (0.12±0.07-mg/kg per hour) and phentanyl (3.7±0.6-mg/kg per hour). The expenditure of droperidol was virtually the same in both groups.

Analysis of the STH secretion dynamics revealed that maximal amounts were secreted in both groups during the most traumatic stage, measuring respectively 3.88±0.55 nmole/l and 3.34±0.64 nmole/l. These values did not differ significantly from each other and did not exceed the level, which could be observed in healthy individuals under condition of psychological stress.

Prolactin concentrations in both groups were increased as compared with the initial value, however, during the traumatic stage, it did not differ significantly from the value registered in the operating room before the beginning of anesthesia initiation.

Cortizole level was also elevated during the most traumatic stage of operation, this elevation being somewhat more pronounced in group I as compared with group II, i.e., the cortizole contents reached 240.3±12.6 nmole/l and 184.0±24.4 nmole/l respectively (p <0.05).
ACTH concentrations gradually decreased in both groups, the minimal value in group I having been reached during the traumatic stage. Examination of STH, prolactin, cortizole, and AGTH secretion has demonstrated that in both groups the changes were going in the same direction. During the operative intervention, hemodynamic parameters in group I displayed greater stability as compared with those of group II in which the elevations of arterial blood pressure and tachycardia required pharmacological correction.

In conclusion, anesthesia with the use of TEA provides a greater degree of patient protection from surgical aggression during the operations for laryngeal tumors as compared with that using NLA. TEA added to the complex of anesthesiological means seems to represent a method of choice for this patient category.
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART II -- APPLICATION OF A NEW METHOD OF TRANSCRANIAL ANALGESIA IN ANESTHESIOLOGY

TRANSCRANIAL ELECTROANALGESIA IN PATIENTS; WITH INJURED PERIPHERAL NERVES

R. I. Voitenko, G. S. KOKIN, and S. M. Kapustin,
Scientific Research Neuro-surgical Institute, Leningrad

A new method of transcranial electroanalgesia (TEA) was used as a main component in 68-cases of operative intervention on the shoulder plexus and the peripheral nerves of the limbs. Narcotic analgesics and neuroleptics were completely excluded, and the gaseous narcotic mixture of nitrous oxide with oxygen at a ratio of 1:1 was employed throughout the operation. By the end of the operation, TEA and nitrous oxide had been discontinued, and the patients immediately restored their consciousness and adequate breath. Early in the postoperative period, the patients were sufficiently active and did not complain of severe pain at the site of operation wound, which was probably due to the analgesic after-effect induced by TEA.

Thus, application of TEA as a component of anesthesia allows to perform successfully the operations, which are accompanied by a marked pain stimulation. Analysis of changes in arterial blood pressure and cardiac rate during the different operation stages in our patients confirmed the fact that hemodynamic parameters were stabilized and, at the same time, provided an evidence that the analgesic effect produced by TEA was an adequate one for the patients examined. This method allows [us] to exclude narcotic analgesics and neuroleptics and to use 20-times lesser concentration of nitrous oxide. It should be added to the qualities of this method that it is followed by rapid restoration of consciousness and adequate breath as well as by patients’ high activity during the postoperative period and the presence of residual analgesia. In addition, application of TEA is of great importance for those patients who have contraindications for the drugs usually employed for pharmacological anesthesia.

TEA was used also for arresting pain syndrome. 40-patients were treated for pain syndrome. The course of treatment usually consisted of 7 to 9-sessions. The character of pain syndrome was evaluated by the presence of smarting nuance of pain, phantom limb pain, nocturnal pain, disturbances of sleep, and other details. Subjective evaluation of pain intensity was carried out using the five-point scale. The session was considered to be successful if the pain level was lowered by not less than 2-points and analgesia lasted for not less than 3-hr.

In our experience, TEA sessions appeared to be highly efficient since 80.2% of them were accompanied by a marked decrease in pain, which occurred immediately during the session and persisted for 9 to 12-hr in average. Repeated TEA sessions did not lead to a stable pain relief in this patient group but these repeated sessions resulted in that the patients more easily tolerated the inpatient examination and the period of transient pain aggravation after the operation. TEA allowed [us] to reduce the amounts of analgesics and somnifacients administered to the patients and to arrest completely all the associated pain manifestations of other origins.
In general, the examined method of TEA is an effective method for combating pain in patients with injured peripheral nerves during both operative and conservative treatment.

*Studies continue on the next page*
Among the operative interventions performed in the traumatological and orthopedic clinic, an important place is occupied by operations on the hip joint and on the proximal end of the femur. These operations are characterized by high traumaticity and extensive wound surface, which lies in the reflexogenic zone as well as by considerable blood loss of up to 1,500-l and duration of more than 1.5 to 2-hr.

One of the most common methods of anesthesia support for these operations is represented by multi-component narcosis involving fluothane and neuroleptanalgesics together with background nitrous oxide inhalation and artificial ventilation of the lungs. We administered such a method to 135-patients (group I). Hemodynamic parameters were observed to be unstable in the course of intervention, while during the postoperative period not infrequently a long-lasting respiratory depression occurred which required an adequate correction.

Our aim was to develop a method for general anesthesia such as to prevent undesirable side effects produced by narcotic drugs and narcotic analgesics in patients with orthopedic disorders.

In 136-patients (group II) combined anesthesia was performed which included the subnarcotic doses of sodium oxybutyrate (50 to 60-mg/kg) and droperidol (0.1 to 0.15-mg/kg) as well as transcranial electroanalgesia by means of combined stimulation with direct current and impulse current at an impulse frequency of 77 to 78-Hz, impulse duration of 3.5 to 4-ms, and nitrous oxide inhalation. Narcotic analgesics were not used either for premedication or for potentiation of anesthesia. Operations were carried out under condition of either artificial ventilation of the lungs or maintained spontaneous breath. In the latter case, no respiratory depression was observed. All patients recovered from narcosis rapidly (within 5 to 7-min) and calmly. Immediately after the operation and during the first day after the operation 85% of patients did not require administration of narcotic analgesics. There was no postnarcotic depression so that patients became active early in the postoperative period. Not a single case of dysuria or marked gastrointestinal tract paresis could be registered.

For objective evaluation of the efficiency of these two methods of anesthesia, immunoresponsiveness indices were studied. During the postoperative period, a marked transient immunodepression of different T-cell populations was observed in group I patients, which evidenced a decrease in immuno-responsiveness and could be due to the insufficient protection from surgical aggression. In group II patients, the absence of inhibitory effect of the drugs employed as well as the adequacy of anesthesiological protection prevented the decrease in immuno-responsiveness.
In conclusion, the application of electrostimulation analgesia allows [us] to exclude completely the narcotic analgesics during operation, to decrease significantly the expenditure of neuroplegics, and to use the single subnarcotic doses of sodium oxybutyrate, which would be sufficient to support a 2- to 3-hr operation. The adequacy of anesthesia provides the maintenance of the immune response during the postoperative period following traumatic interventions in patients with orthopedic disorders and injuries.

*Studies continue on the next page*
A NEW METHOD OF TRANSCRANIAL ANALGESIA

PART II – APPLICATION OF A NEW METHOD OF TRANSCRANIAL ANALGESIA IN ANESTHESIOLOGY

EXPERIENCE WITH TRANSCRANIAL ELECTROANALGESIA AS A COMPONENT OF ANESTHESIOLOGICAL SUPPORT IN PATIENTS WITH EXTRA-PULMONARY TUBERCULOSIS LOCALIZATION

A. I. Vyskubova and V. I. Yuferov,
Scientific Research Institute of Phthisiopulmonology,
RSFSR Ministry of Public Health, Leningrad

Radical-and-plastic operations for the treatment of patients with extrapulmonary localization of tuberculosis are of great importance for the rehabilitation of these patients.

Taking into account the high traumaticity of operative intervention as well as the grave original status of patients including tuberculosis intoxication, deformity of the thorax, and respiratory and cardiac insufficiency in the majority of patients the choice of a conservative method of anesthesiological support would be of great importance for the rehabilitation of patients with extrapulmonary tuberculosis.

Method of transcranial electroanalgesia (TEA), which has been used at our Institute since October 1985, can be regarded as an alternative method of anesthesia aid. TEA will produce the analgesic effect adequate to the operative trauma. Application of this method allows to exclude pharmacological aggression since neuroleptic drugs are not administered in this case.

In addition, there is no hypoventilation early in the postoperative period since the postnarcotic depression is absent.

Throughout the period of clinical trial concerning TEA, an anesthesia was delivered in 34 cases of operative intervention in patients with extrapulmonary localization of tuberculosis. A group of 15 patients operated on different regions of the spine for tuberculosis spondylitis was examined in more detail.

Evaluation of changes in the hemodynamic parameters during the most traumatic stages of the operation was performed. Statistical analysis revealed the following facts: at the moment of dissection there was no significant changes in pulse and arterial blood pressure; at the moment of the most traumatic stage there was a tendency towards decrease in pulse rate and arterial blood pressure as compared with the initial values; and, additionally, according to the clinical assessment, there was no hypoventilation in patients early in the postoperative period.

Thus, the method of TEA used as a component of anesthesia support for radical-and-plastic surgery on different region of the spine in patients with extrapulmonary localization of tuberculosis provides a sufficient analgesic effect and a reliable neuroautonomic blocking during the operative intervention.

The exclusion of pharmacological aggression during anesthesia and the absence of hypoventilation early in the postnarcotic period allow to recommend the method of TEA for anesthesiological support of the operative interventions in patients with tuberculosis spondylitis of the spine associated with respiratory and cardiac insufficiency.
Methods, which are in current use for anesthesia, do not always meet the requirements of pediatric orthopedic practice. Congenital pathology of the skeleton, which often requires a multi-stage surgical treatment, is not infrequently associated with abnormal development of inner organs. The latter circumstance causes problems for application of toxic haloid-derived anesthetics. Peridural [epidural] anesthesia cannot be used both because of abnormalities of the spine and in connection with frequent changes in patients position on the operating table. Employment of the method of neuroleptanalgesia in the course of long-lasting operations makes it necessary to administer high doses of narcotic analgesics and myorelaxants, while calypsol anesthesia will lead to the development of allergic response as well as to the increase in blood loss due to the elevation of arterial blood pressure.

Having taken all the above considerations into account, we attempted to evaluate the expediency of application of a new method of transcranial electroanalgesia (TEA) proposed by V. P. Lebedev at al. (1984) during orthopedic operations in children. TEA was used as a component of anesthesia support for the operations performed on the bones of the pelvis, the femur, and the hip joint as well as during the operations for finger grafting in the children of school age (from 8 to 15-years). We examined 32 cases of anesthesia lasting from 1 to 8-hr.

The following techniques were used in our study. Premedication was performed using 0.1% atropin solution, antihistaminic drug, and diazepam derivative at the doses recommended for each patient’s age. TEA was initially performed at total current value of 3 mA during the slow introduction of 1% sodium thiopental solution until the level I of the surgical stage of anesthesia had been reached. Subsequently, under spontaneous ventilation, the current value was increased up to 12 mA and 0.5% relanium solution was introduced at a dose such as to give 0.1-ml per year of child’s age. Ratio between galvanic and average impulse current values was 2:1, and impulse frequency was 77-Hz. Inhalation of nitrous oxide mixed with oxygen at a ratio of 1:1 was continued throughout the operation period.

If artificial ventilation of the lungs (AVL) was required, droperidol solution was added to premedication. During initial narcosis droperidol was also used. Myorelaxants were administered at usual doses. The total current value reached 15 mA during AVL.

It usually took 10-min from the beginning of TEA to achieve analgesia sufficient for operation. Narcotic analgesics were not used. Moreover, administration of narcotic analgesics was not required during the first 5 to 8-hr after the operation, although the children usually become irritated 4-hr after the operation; they can cause damage to their plaster bandages and require analgesia.
No complications could be observed during narcosis or early in the postoperative period. Children did not complain of headache or nausea. In some patients, local skin hyperemia occurred at the sites of electrode attachment, which disappeared several hours later and was not accompanied by itch and did not require additional treatment.

During anesthesia, respiratory rate increased by 2 to 4 acts per minute as compared with the initial value. Hemodynamic parameters were stable even during the operations, which were associated with significant blood loss. In the latter cases, hemodynamic parameters were more stable when TEA was used as compared with the similar operations during which neuroleptarialgesia was employed. It should be noted that these parameters were characterized by high stability early in the postoperative period after major operations on the pelvis, which were supported by TEA, notwithstanding the fact that such operations, under condition of employment of other anesthesia methods, are usually associated with postoperative tachycardia and instability of arterial blood pressure.

As a whole, the method of transcranial electroanalgesia seems to be promising as a component of anesthesia support in pediatric orthopedic practice and needs further investigation and extensive application.
EXPERIENCE WITH THE APPLICATION OF A NEW METHOD OF TRANSCRANIAL ELECTROANALGESIA UNDER CONDITIONS OF THE TRAUMATOLOGICAL DEPARTMENT OF A DISTRICT HOSPITAL

A. A. Lobzhanidze and Ye. A. Korneva,
Institute of Experimental Medicine of the USSR Acad. Med. Sci., Leningrad

It is known that opioid peptides may exert a manifold influence on the processes, which determine specific and nonspecific resistance of the organism. There is an increasing evidence that the peptidergic structures in the CNS may participate directly in the nervous regulation of protective responses or serve as a source of opioid peptides, which are released into the cerebrospinal fluid and blood (Lebedev et al., 1986). Thus, not only the analgesic but also the therapeutic effect can be observed.

The opioid peptide-induced analgesic effects are well known at the same time, there is much less information concerning the fact that the stimulation of opioid peptide release plays a certain role in the development of a protective response of the organism to injuring factors and accelerates the healing of injuring tissues (Ilyinski et al., 1984).

It was shown that transcranial electroanalgesia caused two kinds of effects, i.e., analgesia and stimulation of the organism’s protective mechanisms. These effects are usually associated with the release of large amounts of neuropeptides such as endorphin. Thus, the application of transcranial analgesia at the Hospital suggested the two possible affects, those of pain relief and of protective mechanism activation.

46-patients were observed who represented the following clinical groups: postoperative patients; patients suffering vertebral osteochondrosis; patients with phantom limb pain after amputation of the limb; and patients with peripheral neuritis.

In all patients a marked analgesic effect could be observed after the end of treatment course. This effect was expressed in pain relief, motor function restoration, and increase in patients’ motor activity. In 45% of cases a therapeutic effect could be also observed, i.e., not only was pain reduced but there was also a recovery from underlying disorder after a single course of transcranial electroanalgesia (5-sessions divided by one-day intervals).

There were no recurrences during the whole 1-year follow-up period.

In a number of patients, the main objective of transcranial electroanalgesia application was to achieve the analgesic effect, which allowed the management of patients undergoing pain syndrome-inducing surgery without administration of any narcotic and non-narcotic analgesics. Thus, the adverse drug-induced effects could be avoided.

In our experience, the method of transcranial electroanalgesia is useful for routine practical application at the Traumatological Department.
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