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STUDYING STRESS REACTIONS IN THE BLOOD OF PATIENTS WITH COMBINED MID-FACIAL TRAUMA AND APPLICATION IN REHABILITATION OF TRANSCRANIAL ELECTRICAL STIMULATION

Purpose of the study. The aim of this research was to compare the effectiveness of transcranial electrical stimulation to normalize the regulatory functions of the CNS in the postoperative period of treatment of patients with bone injuries of the middle face. **Research methods.** The study was performed in 47 patients with combined mid-facial trauma, characterized by the presence of mild traumatic brain injury (concussion, brain contusion of mild severity) and severe injuries of the facial skeleton – 1, 3, 4, 7 classes according to the Yu.I. Bernadsky classification. After surgical treatment, all patients were divided into two groups. Conservative treatment according to the traditional scheme described above was used for rehabilitation of patients in the control group (22 patients). The same scheme was used for the treatment of patients of the main group (25 patients), but it was supplemented by a course of transcranial electrical stimulation, which was performed using a low-frequency electrotherapy device “Radius-01 FT”. The parameters of transcranial electrical stimulation were established according to the literature of similar studies [20; 21; 22], and were DPS = 5%, 70 Hz, 0.11 ms with a session duration of 35 minutes 1 time per day with a course of treatment of 10 days. The 7th and 14th days were chosen as the terms of observation of the effect of its influence on the body’s resistance to stress factors, while hematological studies were selected as indicators to determine the content of β -endorphins, ACTH and cortisol, and to calculate the Garkavi stress index. **Scientific novelty.** Studies have shown that the use of transcranial electrical stimulation helped to normalize the tone of anti-stress defense mechanisms, stimulated endorphinic structures of the brain and reduced the intensity of pain in patients with combined mid-facial trauma. Already on the 7th day, the content of stress-limiting hormones β -endorphins in the plasma of the main group patients was higher compared to that of the control (15.4 ± 1.8 pg / ml to 12.73 ± 1.6 pg / ml with $g > 0.05$). **Conclusions.** The obtained data indicate a positive therapeutic effect of transcranial electrical stimulation on the stress-limiting endogenous opiate system.

Key words: transcranial electrical stimulation, skull-brain trauma.



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ДОСЛІДЖЕННЯ СТРЕСОВИХ РЕАКЦІЙ У КРОВІ ХВОРИХ З ПОЄДНАНОЮ ТРАВМОЮ СЕРЕДНЬОЇ ЗОНИ ОБЛИЧЧЯ ТА ЗАСТОСУВАННЯ В РЕАБІЛІТАЦІЙНИЙ ПЕРІОД ТРАНСКРАНІАЛЬНОЇ ЕЛЕКТРОСТИМУЛЯЦІЇ

Метою досліджень було порівняння ефективності застосування транскраніальної електростимуляції для нормалізації регуляторних функцій ЦНС у післяопераційному періоді лікування хворих із травмами кісток середньої зони обличчя. **Методи дослідження.** Дослідження проводилися у 47 хворих із поєднаною травмою середньої зони обличчя, для якої була характерна наявність легкого черепно-мозкового ушкодження (струс головного мозку, забій головного мозку легкого ступеня тяжкості) та тяжке пошкодження лицьового скелета (1, 3, 4, 7 класи за класифікацією Ю.І. Бернадського). Усі хворі після проведеного відповідного хірургічного лікування були поділені на дві групи. Для реабілітації хворих контрольної групи застосовували консервативне лікування за традиційною схемою (22 хворих). Така сама схема застосовувалася і при лікуванні хворих основної групи (25 хворих), але додатково вона доповнювалася курсом транскраніальної електростимуляції, яку проводили за допомогою низькочастотного приладу електротерапії «Радіус-01 ФТ». Параметри роботи транскраніальної електростимуляції становили ДПС = 5%, 70 Гц, 0.11 мс із тривалістю сеансу 35 хв 1 раз на добу з курсом лікування 10 днів. Термінами спостереження ефекту її впливу на резистентність організму до дії стресових факторів було обрано 7 та 14 добу, як показниками – гематологічні дослідження визначення вмісту β -ендорфінів, АКТГ та кортизолу, віднімання стресового індексу Гаркаві. **Наукова новизна.** Дослідження показали, що застосування транскраніальної електростимуляції сприяло нормалізації тону механізмів антистресового захисту, стимулювало ендорфінові структури головного мозку і зменшувало інтенсивність больового синдрому у пацієнтів з поєднаною травмою середньої ділянки обличчя. Вже на 7-му добу вміст стрес-лімітуючих гормонів β -ендорфінів у плазмі крові хворих основної групи був вищим порівняно з контрольною ($15,4 \pm 1,8$ пг/мл до $12,73 \pm 1,6$ пг/мл з $p > 0,05$). **Висновки.** Отримані дані свідчать про позитивний терапевтичний ефект транскраніальної електростимуляції на стрес-лімітуючу ендогенну опіатну систему.

Ключові слова: транскраніальна електростимуляція, черепно-мозкова травма.

Introduction. The data analysis of literature resources indicates a fairly high percentage of injuries of the middle area of the face, which makes up from 33% to 55% of all such injuries. They are mainly caused by serious

traffic accidents (up to 89.5%) and domestic injuries. All facial injuries have a number of common features. In 86–100% of cases, they are combined with a closed traumatic brain injury [4; 5].



Common features of such cases are violated vascular trophism of brain with the occurrence of reflex spasm and vasodilation of blood vessels, slow blood flow and increased capillary penetration [17]. Against this background, there is a change in the secretion of hormones of the hypothalamic-pituitary system, adrenocorticotrophic and somatotrophic hormones [19]. There is also a violation of the regulatory function of the central nervous system, in particular, insufficient production of calcitonin, which leads to a slowdown in reparative osteogenesis and prolongation of the post-traumatic rehabilitation period [10; 12].

According to a large number of researchers, along with modern medical treatment, among rehabilitation measures for combined injuries of the middle face and CNS, rehabilitation procedures are of great importance. They could be used at all stages of the disease and can effectively correct certain pathogenetic parts of the process and carry out symptomatic treatment [15; 16; 18].

Recently, much attention has been paid to the use of transcranial electrotherapy, one of the modifications of which is transcranial electrical stimulation. It is established that with its help it is possible to activate opioid structures of the brain and structures of the hypothalamic-pituitary area, to normalize the subcortical structures of the brain, which allows to optimize the synthesis of neurohormones that regulate the organs and systems of the human body [1; 2; 3; 6; 8].

Also at present there is a gradual modification of transcranial electrical stimulation. It has been improved to the type of mesodiencephalic modulation, which is characterized by a selective exposure of the corresponding mesodiencephalic structures of the brain to impulse current with the frequency of 20 to 10,000 Hz with a force of up to 6-8 mA. [13; 14].

This makes it possible to more effectively change the electrical and biochemical activity of the centers of the hypothalamic-pituitary system and translate the body's adaptation system to a much higher functional level. In the acute post-traumatic period, it provides a pronounced nootropic effect and rapid regression of pathological symptoms, disappearance of symptoms of traumatic neuritis of the infraocular and zygomatic

nerves, restoration of sensitivity and improvement of microcirculation of the damaged area [22].

In general, transcranial electrical stimulation, which is minimally invasive, can effectively influence the regulatory mechanisms of the body, reduce the treatment and hospitalization course. It can be performed by medical professionals of any qualifications and even patients themselves [9].

Given the above and significant practical interest in the treatment of patients with combined trauma of the maxillofacial area, this **scientific work** aims at comparing the effectiveness of transcranial electrical stimulation to normalize the regulatory functions of the CNS in the postoperative period of treatment of patients with middle face bone injuries.

Materials and methods. In order to comply with the principles of evidence-based medicine, which requires minimal differences between the comparative groups, patients who were hospitalized in the department of maxillofacial surgery with middle facial fractures, which can be attributed to the third type of combined middle facial injury according to the classification of A.P. Fraerman and Y.E. Telman, ie with a mild traumatic brain injury and severe facial skeleton injuries, were selected for research.

This type of combined mid-facial trauma included 47 patients with mild brain injury (concussion, brain contusion of mild severity) and severe injuries of the facial skeleton – 1, 3, 4, 7 classes according to the classification of Yu.I. Bernadsky.

All treatment procedures were agreed with the neurosurgeon, who performed daily monitoring of the effectiveness of treatment of such patients. The conservative treatment regimen was also prescribed in consultation with a neurosurgeon. The development of an advanced complex was based on the traditional version of therapy. It included standard antibiotic therapy (clindamycin – 600 mg twice a day for 7–8 days), analgesic and anti-inflammatory therapy (ketoprofen – 100 mg twice a day for 5–6 days), anti-edema therapy (L-lysine escinate – intravenously 5–10 ml of the drug).

After surgical treatment, all patients were divided into two groups. Conservative treatment according to the traditional scheme described



above was used for rehabilitation of patients in the control group (22 patients). The same scheme was used for the treatment of patients of the main group (25 patients), but it was supplemented by a course of transcranial electrical stimulation, which was performed using a low-frequency electrotherapy device “Radius-01 FT”. The parameters of transcranial electrical stimulation were established according to the literature of similar studies [11; 20; 21], and were DPS = 5%, 70 Hz, 0.11 ms with a session duration of 35 minutes 1 time per day with a isol was performed by immunochemical method using electrochemiluminescent detection on an analyzer with a test system Cobas 6000, Roche Diagnostics (Switzerland). Reference values – 6.2–19.4 mcg / dl. The conversion factor $\mu\text{g} / \text{dl} \times 27,586 = \text{nmol} / \text{l}$.

Determination of ACTH (pg / ml) was performed by immunochemical method with chemiluminescent detection (CLIA). Immulite analyzer and test system (Siemens AG), Germany, were used.

Quantitative determination of the marker of the anti-stress system of β -endorphin in blood plasma (pg / ml) was performed by enzyme-linked immunosorbent assay using the kit “Uscn Life Science Inc.” (USA).

The type of general nonspecific adaptive response of the organism under conditions of traumatic stress was determined by the percentage of lymphocytes in the leukocyte formula, by their ratio to the percentage of segmental neutrophils – the adaptation index Garkavi L.H.:

Criteria for adaptive reactions:

a) stress response: lymphocytes less than 20%, adaptation index less than 0.3;

b) training reaction: lymphocytes – 21–27%, adaptation index – 0.31–0.50;

c) reaction of quiet activation: lymphocytes – 28–33%, adaptation index – 0.51–0.7;

d) reaction of increase d activation: lymphocytes – 34–42%, adaptation index – 0.71–0.90;

e) reactivation reaction: lymphocytes higher than 43%, adaptation index higher than 0.90;

e) defective adaptation reaction: peripheral blood leukocytes – $4.0 \cdot 10^9 / \text{l}$ and less.

The level of reactivity was determined by the degree of deviation from the norm of the blood formula elements: high, medium, low and very low.

The results were analyzed according to the standard method of descriptive statistics using

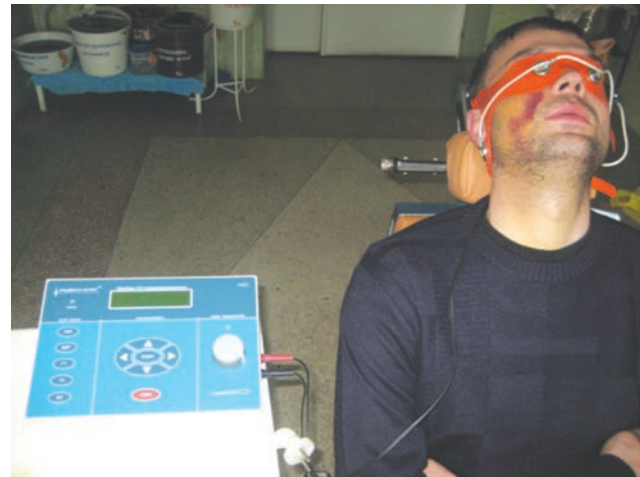


Fig. 1. A session of transcranial electrotherapy in a patient with traumatic bone injury of the middle face area

a personal computer with the appropriate software package “StatSoft Statistica 10” installed. For statistical characteristics of the obtained data of each of the experimental animals, the following indicators were calculated: mean value (M) \pm standard error (m).

Comparison of mean values in different groups was performed using the classical parametric t-test. When comparing the results, we used the estimation of differences by a method adequate for small samples, using the table of Student’s criterion. The differences were considered significant at $p < 0,05$.

The research results. The use of electrical stimulation of the brain in patients with combined trauma in the postoperative period increases the level of β -endorphins in blood plasma, which indicates the activation of the stress-limiting endogenous opiate system of the body. In patients with type 3 combined injury, the content of β -endorphins was higher than normal on the 7th day in the control ($12.73 \pm 1.6 \text{ pg} / \text{ml}$) and the main groups ($15.4 \pm 1.8 \text{ pg} / \text{ml}$). On the 14th day, the growth of β -endorphins stopped in both clinical groups. High levels of β -endorphins in patients with type 3 combined injury are due to the lack of violations of regulatory mechanisms at the level of the hypothalamic-pituitary system, which are present in patients with severe trauma. The obtained data clearly indicate a positive therapeutic effect of dynamic electrical stimulation on the stress-limiting endogenous opiate system (Table 1).



Table 1
Dynamics of the content of β -endorphins in the plasma of patients during postoperative rehabilitation

Clinical group	Stress-limiting system β -endorphins (ng/ml)	
	Day 7	Day 14
indicator healthy person	5.31±1,28	5.31±1,28
control	12,73±1,6 $p_1 < 0,05$	12,8±1,8 $p_1 < 0,05$
main	15,4±1,8 $p_1 < 0,05$ $p_2 > 0,05$	13,13±1,9 $p_1 < 0,05$ $p_2 > 0,05$

* Note: p_1 – comparison of obtained indicators with the indicator of a healthy person; p_2 – statistical significance was compared between the control and main groups.

Analysis of the stress- releasing body system indicators showed that the content of ACTH and cortisol gradually decreased in all patients during postoperative rehabilitation. However, it was statistically established that the rates of patients who received TES stimulation dropped to normal much faster. In patients with mild trauma and severe trauma of the zygomatic-orbital complex, the content of ACTH (35.67 ± 3.42 pg/ml) and cortisol (309.9 ± 12.3 nmol / l) on the 14th day was significantly lower in the main group than that in the control (ACTH – 44.62 ± 4.37 pg / ml; cortisol – 364.4 ± 16.3 nmol / l). These results can be explained by the severity of injuries that caused disturbances in the hypothalamic-pituitary system. The use of transcranial electrical

stimulation helped to regulate the release of stress-releasing hormones into the blood and reduce the level of stress and anxiety in patients in the postoperative period (Table 2).

When assessing the stress index, on the 7th day after surgery, the indicators were found to be less than 0.3. This indicates that most patients with combined trauma develop a stress response to the trauma, which indicates the maximum stress of the body non-specific adaptation systems. It should be noted that in patients of the main group, the Garkavi index on the 7th day showed a training reaction. Examination on the 14th day revealed that stress reactions stopped and turned into a training response in both clinical groups with slightly higher rates in the main group (control group – 0.41 ± 0.05 ; main group – 0.44 ± 0.040) (Table 3).

Table 3
Dynamics of the stress index of patients during postoperative rehabilitation

Clinical group	Garkavi stress index	
	Day 7	Day 14
indicator healthy person	0,35 ± 0,09	0,35 ± 0,09
control	0,27±0,03 $p_1 > 0,05$	0,41±0,05 $p_1 < 0,05$
main	0,29±0,03 $p_1 > 0,05$ $p_1 > 0,05$	0,44±0,04 $p_1 < 0,05$ $p_1 < 0,05$

* Note: p_1 – comparison of obtained indicators with the indicator of a healthy person; p_2 – statistical significance was compared between the control and main groups.

Table 2
Manifestations of stress reactions in the blood of patients with combined trauma of the middle facial zone of varying severity

Clinical group	Stress- releasing system			
	ACTH (pg / ml)		Cortisol (nmol / l)	
	Day 7	Day 14	Day 7	Day 14
indicator healthy person	34,18 ± 1,79	34,18 ± 1,79	299.83 ±10,57	299.83 ±10,57
control	47,53±5,34 $p_1 < 0,05$	44,62±4,37 $p_1 < 0,05$	379,5±16,7 $p_1 < 0,05$	364,4±16,3 $p_1 < 0,05$
main	39,69±3,46 $p_1 > 0,05$ $p_2 > 0,05$	35,67±3,42 $p_1 > 0,05$ $p_2 > 0,05$	362,4±15,9 $p_1 < 0,05$ $p_1 > 0,05$	309,9±12,3 $p_1 > 0,05$ $p_2 < 0,05$

* Note: p_1 – comparison of obtained indicators with the indicator of a healthy person; p_2 – statistical significance was compared between the control and main groups.



Analysis of the obtained results. Our studies indicated that the content of stress-limiting hormones β -endorphins in the plasma of the main group patients on the 7th day was higher than that of the control (15.4 ± 1.8 pg / ml to 12.73 ± 1.6 pg / ml with $p > 0.05$), indicating a positive therapeutic effect of transcranial electrical stimulation on the stress-limiting endogenous opiate system. By the 14th day, the indicators of control and the main group had already differed little from each other and tended to decrease.

The contents of ACTH and cortisol, which mark the stress-releasing system, were characterized by a moderate increase on the 7th day with a gradual decrease on the 14th day. Thus, in the control group they were as follows: ACTH – 47.53 ± 5.34 pg/ml and 44.62 ± 4.37 pg/ml, cortisol – 379.5 ± 16.7 nmol / l and $364.4 \pm 16, 3$. A similar trend could be observed in the examination of the main group patients, but it was statistically established that these indicators during TES stimulation decreased to normal much faster (ACTH – 39.69 ± 3.46 pg / ml and 35.67 ± 3.42 pg / ml, cortisol – 362.4 ± 15.9 nmol / l and 309.9 ± 12.3 nmol / l).

The obtained data will allow to assert that transcranial electrical stimulation provided regulation of the release of stress-releasing hormones into the blood and reduction of stress levels and anxiety in patients in the postoperative period.

These data were confirmed by the indicators of the Garkavi stress index. In all patients on the 7th day of observation, this figure was less than 0.3. Thus, in the control group it made up 0.27 ± 0.03 , while in the main – 0.29 ± 0.03 , which indicated that such patients develop a stress response to trauma with the maximum stress of the body non-specific adaptation systems.

Examination on the 14th day showed that stress reactions stop and turn into a training reaction in both groups. However, in the main group, these phenomena occur more intensely, as indicated by the digital data of the Garkavi index (0.41 ± 0.05 in the control to 0.44 ± 0.04 with $p < 0.05$ in the main group).

Conclusions. The post-traumatic period in patients with the middle facial trauma is

accompanied by stress disorders, confirmed by hematological studies with a significant increase in stress markers (ACTH and cortisol) and an insignificant increase in anti-stress factors in the blood. Insufficient stress-limiting function of the hypothalamic-pituitary system slows down the healing process and requires appropriate correction.

To improve the postoperative rehabilitation period, it is recommended to supplement the traditional scheme of conservative treatment with 10 sessions of transcranial electrical stimulation in the mode of DPS=5%, 70Hz, 0.11 ms with a session duration of 35 minutes once a day. This scheme acts on the main pathogenetic links of complications during the postoperative period of treatment of patients with middle facial fractures, is minimally invasive, easily tolerated by patients, and has a limited number of contraindications.

The consequence of combined mid-facial trauma is the occurrence of a stress response, which manifests itself in the imbalance of CNS regulatory function. The use of transcranial electrical stimulation helped to normalize the tone of anti-stress defense mechanisms, stimulated endorphin structures of the brain and reduced the intensity of pain in patients with combined mid-facial trauma. Already on the 7th day, the content of stress-limiting hormones β -endorphins in the plasma of patients of the main group was higher compared to that of the control (15.4 ± 1.8 pg / ml to 12.73 ± 1.6 pg / ml with $p > 0.05$), indicating a positive therapeutic effect of transcranial electrical stimulation on the stress-limiting endogenous opiate system.

Prospects for further research. Stress that occurs in patients with combined mid-facial trauma in response to trauma causes significant changes in the stability of the balance of the sympathetic and parasympathetic divisions of the autonomic nervous system, which is characterized by impaired cardiovascular and regional blood flow. The application of the proposed course of transcranial electrical stimulation in postoperative rehabilitation helps to reduce these manifestations,



helps to restore the conduction of nerve trunks, has an anti-edematous effect on the soft tissues of the infraorbital area and improves hemodynamics of the infraorbital artery and vein. Improving

this method and finding new modes of activity of the centers of the hypothalamic-pituitary system can significantly improve the quality of treatment of patients with this pathology.

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