Possibilities of Applying Non-invasive Multichannel Electrical Stimulation Technology for Treatment Neuropsychiatric Diseases

Timur S. Petrenko[1][a], Vladimir S. Kublanov[1][b], Konstantin Ju. Retyunskiy[1][c] and Roman A. Sherstobitov[2][d]

[1]*Ural Federal University, Yekaterinburg, Russian Federation*

[2]*Ural State Medical University, Yekaterinburg, Russian Federation*

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Abstract: The article discusses some of the mechanisms of clinical effects when using the technology of non-invasive multichannel electrical stimulation of the neural formations of the neck in patients with diseases of the central nervous system of the neuropsychiatric profile. When implementing this technology in all clinical examples, "SYMPATHOCOR-01" device was used, which provides stimulation of neural formations of the neck using a spatially distributed field of monopolar current pulses.

1 INTRODUCTION

The rapid spread throughout the world of diseases of the central and peripheral nervous system determines the relevance of the search for effective pathophysiologically-based therapeutic and rehabilitation approaches to their correction. In most cases, the pathogenetic links of such diseases are realized through dysregulation of the autonomic nervous system (Licznerski, Duman, 2013). Particularly relevant today are diseases associated with organic damage to the central nervous system.

Existing methods of treatment of central nervous system diseases suggest the use of pharmacological agents with high risks of unwanted and side effects (Watanabe et al, 2010). An alternative approach may be to stimulate the structures of the central and peripheral nervous system using multi-electrode systems of neuroelectrostimulation . The activation of different parts of the nervous system in this way allows you to get a variety of clinical effects, including may affect somatic processes in the body (Danilov et al, 2015).

To create effective medical technologies in the treatment of neuropsychiatric disorders, it is necessary to understand the physiological mechanisms of the formation of the clinical result, depending on the therapeutic agents used.

This work presents the results of studies of medical technologies in which the therapeutic effect is achieved through the use of a neuroelectrostimulator "SYMPATHOCOR-01" device (Kublanov, Babich, Petrenko, 2018)

2 RESULTS OF CLINICAL STUDIES

2.1 Attention Deficit Hyperactivity Disorder (ADHD)

In the period from 2007 to 2014, we conducted a study for children with ADHD. Participated 90 children of both gender and ages from 4 to 10 years that have clinic features of the ADHD syndrome (according to the ICD-10). The degree of the ADHD symptoms was estimated by the psychometric scale ADHD-RS-IV (Attention-Deficit Hyperactivity Disorders Rating Scale IV). The attention level was estimated by means of the psycho-physiological test

[a] https://orcid.org/0000-0001-7328-9894
[b] https://orcid.org/0000-0001-6584-4544
[c] https://orcid.org/0000-0003-1302-483X
[d] https://orcid.org/0000-0002-090-407X

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T.O.V.A. (the Test Of Variability Of Attention). Impairments of the brain bioelectric activity (of children with the ADHD) were verified by the electro-encephalographic investigation. In such children, increasing the theta- and delta-activity was observed and/or impairment of the main (alpha) rhythm under the loading tests. For treating children, a complex therapy was applied: in group I (of 37 participants), neuromethabolic remedies were used; in group II (of 55 participants), neuromethabolic was used together with the neurostimulation device.

The best result has been achieved in the second group of children, in which during the treating process, both the complex medicated therapy and neurostimulation were used. The dynamic of ADHD overall score was: in I group from 2.11±0.34 to 1.88±0.11; in II group from 2.08±0.45 to 1.22±0.17. The dynamic of attention level by TOVA was: for omission error in I group from 28.5±4.3 to 21.1±2.5 and in II group from 32.5±4.3 to 8.7±2.7; for commission error in I group from 19.2±4.9 to 18.8±2.2 and in II group from 23.5±4.3 to 8.7±3.1. Catamnesis observation after children of the second group has proved stability of the achieved results two years later from the treatment beginning (Kublanov, Petrenko, Retyunskiy, 2016).

2.2 Psychosomatic Disorders

In 2018 we conducted study for children with psychosomatic disorders. Participated 83 children of both sexes from 5 to 14 years old with following diagnosis: bronchial asthma (n = 34), atopic dermatitis (n = 27), gastroesophageal reflux disease (n = 22). Data on relevant diseases were evaluated by clinical methods. Baseline ANS was assessed by the heart rate variability (HRV). All children were randomly divided into two groups (n1 = 41; n2 = 42). The entire observation period was 21 days. Both groups received standard medical therapy prescribed by a pediatrician. The second group was given additional neurostimulation daily therapy for 2 weeks. Evaluation of the state of children after the observation period was carried out according to the same criteria as the original one.

Clinical trials showed that most children (78%) had increased baseline ANS activity, which correlated with the severity of somatic manifestations. After two weeks of complex therapy improving the clinical condition was observed in most children in the group with neuroelectrostimulation device. This is consistent with the HRV analysis: LF/HF ratio for the first group changed from 7.71±4.54 to 5.82±6.28; for the second group – significantly decreases from 8.21±5.82 to 2.12±4.53.

Adding non-invasive correction of ANS to standard medical therapy allows reducing the condition of children with psychosomatic diseases (Petrenko, 2019).

2.3 Anxiety Disorder

In 2015 we have investigated the effectiveness of the method of dynamic correction of activity of the sympathetic nerves system by using neurostimulation device in comparison of standard medications approach in patients with panic disorder.

The study included 40 patients from clinical base of the Department of Psychiatry of Ural State Medical University with diagnosed 'panic disorder'. All patients were randomly divided into two equal group. Patients from the first group received antidepressant – escitalopram 10mg once daily. Patients from the second received a course of ten procedures of neuroelectrostimulation. The period of therapy and dynamic follow-up was six weeks. The Hamilton (HAM-A) and Sheehan (SPRAS) anxiety scales were used to determine changes in state of patients.

For patients from the first group were follow changes by scales for the six-weeks period: HAM-A (from 26.35±7.53 to 15.35±4.20), SPRAS (from 72.83±21.41 to 39.27±8.13). For patients from the second group: HAM-A (from 27.49±7.32 to 7.30±2.05), SPRAS (from 74.33±23.42 to 24.22±5.29).

The neurostimulation therapy in comparison antidepressant was a faster onset of the therapeutic effect, a faster reduction quantity and severity of panic attacks during the whole period of observation (Petrenko, Retjunskiy, Kublanov, 2018).

2.4 Organic Amnestic Syndrome

In 2016 we conducted study for patient with organic amnesic syndrome. Three patients with clinical organic amnestic syndrome resulting of brain damage (poisoning, alcohol and trauma) held inpatient treatment for at least 12 months in the neurology or psychiatry department without a significantly improvement.

Patients were assessed using the clinical method, neuropsychological scales: Frontal Assessment Batter (FAB), Montreal Cognitive Assessmnet (MCA), Mini-Mental State (MMSE), MRI, EEG, Heart rate variability (HRV). The initial clinical state of the patients was severe, with structural damage on MRI and low rates of neuropsychological tests. As a result of seven Neurostimulation procedures improved significantly neuropsychological assessments: FAB (from 5,7±3,1 to 12±4,0); MCA (from 11,3±3,0 to 16,3±4,0); MMSE (from 15,3±6,2 to 21,3±8,3). EEG comparison analysis showed an increase in power of Alpha waves and power reduction of Delta waves on all leads. HRV comparison analysis showed an increase total power and the change in autonomic balance (Retyunskiy, 2017).

Thus, the resulting clinical effects in the described cases required a thorough study of the mechanisms of action of multichannel electrical stimulation of the nerve formations of the neck. We conducted experimental studies on laboratory animals, as well as fundamental clinical studies using neuroimaging technologies.

3 EXPERIMENTAL RESEARCH

To study changes at the cellular and tissue levels, as well as behavioral functions in 2009-2010. We conducted experimental studies of the effectiveness of stimulation using the above field of current pulses in laboratory rats to correct disorders caused by immobilization stress and ischemia of the leg muscles. For stimulation, the "SYMPATHOCOR-01V" device was used, the parameters of which were modified taking into account the difference in the blood supply system of a laboratory rat with respect to humans (Kublanov et al, 2010).

After exposure to immobilization stress, rats were less likely to switch between elements of an open field polygon, consisting of 25 elements and equipped with a vision system. This was manifested by a decrease in the length of the trajectories of movement and a decrease in the motor activity of rats. The application of the electrical stimulation procedure after immobilization stress was accompanied by the restoration of these characteristics.

Also, stress parameters were noted by blood biochemical parameters (AST, ALT, LDH, MSM), which corresponds to the state of endogenous intoxication. After exposure to current pulses by the field, blood biochemical parameters returned to the level of intact animals.

When studying the morphological picture of sections of ischemic muscle of rats, it was noted that after exposure to electrical stimulation of the cervical ganglia there is a rapid restoration of blood supply due to the growth of capillaries of collateral arterial systems.

Thus, neuroelectrostimulation helps to reduce the negative effects of immobilization stress and ischemic muscle damage, which is accompanied by:

1) at the molecular-cellular level - by a decrease in metabolites and endogenous intoxication products characteristic of stress, which the body does not manage to utilize during immobilization stress and ischemic muscle damage;

2) at the tissue level - stimulation of angiogenesis, restoration of blood supply and contractile apparatus in the ischemic muscle tissue of the hind tibia of rats;

3) at the level of the body - a change in the behavioral reaction, manifested in increased adaptation to immobilization stress (Kublanov et al, 2010).

4 FUNDAMENTAL RESEARCH

Obtaining new knowledge about the mechanisms for implementing the clinical effects of neuroelectrostimulation essentially belongs to the category of basic research. In our case, the studies were performed in the form of clinical cases with a detailed study of the results of functional neuroimaging.

4.1 Study of SPECT and EEG in Patients with Incurable Forms of Epilepsy

Confirmation of nonspecific changes in brain tissue after dynamic correction of the activity of the sympathetic nervous system using the "SYMPATHOCOR-01" device is the result of changes in single-photon emission computed tomography (SPECT) and electroencephalogram (EEG) in patients suffering from epilepsy.

To illustrate, the data of the clinical case of patient D., 20 years old, suffering from a cryptogenic temporomandibular form of epilepsy are presented. Before treatment in patient D., the number of epileptic seizures was 12–16 per month. Before treatment, according to SPECT, the asymmetry of the perfusion marker accumulation between different regions of the cerebral cortex was determined up to 20%. According to the EEG, epileptiform activity in the form of sharp waves and spikes in the frontotemporal regions of variable lateralization, more often on the right. After 5 treatment procedures, patient D. did not have epilepsy attacks for three weeks, and three attacks in the following weeks. Subjective well-being was noted (headaches disappeared, sleep improved, appetite, the level of anxiety and aggressiveness decreased). According to SPECT, in cross sections, the asymmetry of perfusion marker accumulation is up to 6%. According to EEG data, moderate diffuse changes in BEA with signs of increased synchronizing effects of mid-stem structures, epileptiform activity in the form of sharp waves and spikes in the lateral regions of variable lateralization in the left hemisphere, epileptiform activity of the previous localization, but quantitatively less (Kublanov et al, 2004).

4.2 Study of RS-fMRI and Multichannel EEG in Patients with Depressive Disorder

We conducted pilot studies of changes in the functioning of the basic working network of the brain according to functional magnetic resonance imaging of resting state (RS-fMRI). The study involved 10 patients with established depressive disorder. The use of neuroelectrostimulation with the "SYMPATHOCOR-01" device in addition to pharmacotherapy prescribed by a doctor turned out to be more effective according to clinical data (self-test of symptoms of Beck depression, Hamilton depression scale) compared with patients who did not receive electrical stimulation.

According to the analysis of fMRI data after 5 days of neuroelectrostimulation, a significant improvement in the functional connections of the medial prefrontal cortex with other brain regions was noted. This indicates an improvement in connectivity, especially due to the activation of the premotor zones of the cerebral cortex.

The results of an electrophysiological study according to multichannel EEG are consistent with the results of the analysis of functional connectivity. In all clinical cases, after a course of neuroelectrostimulation, a change in the asymmetry of the power distribution of the main EEG rhythms in the direction of harmonization was noted; expansion of variability of activation zones; improving bioelectric synchronization of various parts of the cortex (Kublanov, Petrenko, Efimcev, 2019).

Thus, the results of experimental and fundamental studies made it possible to formulate a theoretical justification for the selection of stimulation targets.

5 THEORETICAL SUBSTANTIATION OF THE CHOICE OF TARGETS OF NEUROELECTRIC STIMULATION

The regulation of many physiological processes in the human body is carried out by the central nervous system (CNS) and the autonomic nervous system (ANS). Centers for the regulation of vital functions are represented by the nuclei of the brain stem, midbrain, bridge and cerebellum, as well as the vegetative nuclei of the spinal cord and brain. Most of the pathways of these centers are located in the neck.

Somatic innervation of the neck is carried out by the cervical spinal nerves, which form a massive cervical plexus, located on the anterolateral surface of the deep muscles of the neck. Front and side, it is covered by the sternocleidomastoid muscle.

The composition of the spinal nerves includes efferent and afferent fibers. Efferent fibers begin from the nuclei of the anterior horns of the spinal cord. Afferent fibers pass through the posterior horns of the spinal cord and end in the sensitive nuclei of the brain stem and reticular formation. The reticular formation is involved in the processing of sensory information: it has a selective activating effect on the cerebral cortex or an inhibitory effect on spinal cord motor neurons, delaying habitual or repeated impulses. Using this mechanism, somatomotor and self-sensitive control, neuroendocrine transduction and coordination of the work of different centers of the brain stem are carried out.

On the deep muscles of the neck is the cervical sympathetic trunk, which is represented by three nodes. Nerve fibers approach the cervical nodes from the autonomic nuclei of the lateral substance of the thoracic spinal cord. Seven main branches departing from the upper cervical node, containing postganglionic fibers and propagating along the external and internal carotid arteries, as part of the fibers of the glossopharyngeal, vagal and sublingual nerves. Thus, the sympathetic innervation of the vessels of the head and neck, the parotid and thyroid glands is carried out (Netter, Frank, 2014).

The middle cervical node (intermittent), located at the level of the VI cervical vertebra at the intersection of the lower thyroid and common carotid arteries. The lower cervical (stellate) node is located above the subclavian artery and behind the vertebral artery. These nodes provide sympathetic innervation of the vessels of the shoulder girdle, spine and meninges of the spinal cord. Cardiac nerves participating in the formation of the cardiac plexus depart from the cervical nodes. From the upper node - the upper cardiac nerve, is involved in the formation of the superficial cardiac plexus. From the middle and lower nodes - the middle and lower cardiac nerves, respectively, involved in the formation of the deep cardiac plexus. With the help of these plexuses, sympathetic regulation of cardiac activity is carried out (Netter, Frank, 2014).

In the course of the internal jugular vein, first the internal carotid, and then the common carotid artery, the vagus nerve is located, forming a neurovascular bundle of the neck. The vagus nerve, being mixed, originates from the motor, sensory and parasympathetic nuclei of the brain stem. The motor nucleus (nucleus ambiguous), common with the glossopharyngeal and accessory nerves, has motor axons that innervate the muscles of the soft palate, pharynx, and larynx.

The dorsal nucleus (nucleus dorsalis) has parasympathetic fibers. Afferent impulses in this nucleus come from the hypothalamus, olfactory system, and autonomic centers of the reticular formation. The efferent impulses of the dorsal nucleus travel through the postganglionic fibers to the smooth muscles of the lungs, heart, and gastrointestinal tract. Thus, parasympathetic regulation of respiration, palpitations and digestion is carried out.

In the area of bifurcation of the common carotid artery, there is a carotid glomerulus, which is a capillary clot with a large number of chemo- and baroreceptors. Impulses from these receptors are transmitted along the glossopharyngeal nerve to the nucleus of the single pathway (nucleus tractus solitarii), common to the facial, glossopharyngeal and vagus nerves. Similar chemoreceptors are located on the aortic arch and transmit their impulses in the composition of afferent fibers of the vagus nerve along the same path. Thus, the regulation of blood pressure and oxygen tension in the blood is carried out (Moore, 2013)

Nerve formations in the neck are closely connected with the brain stem, through which they have bilateral connections with the bridge, midbrain, cerebellum, thalamus, hypothalamus and cerebral cortex. The presence of these connections ensures the participation of nerve formations of the neck in the analysis of sensory irritations, regulation of muscle tone, autonomic and higher integrative functions.

Based on the foregoing, the cervical ganglia of the sympathetic trunk, the cervical plexus of the spinal nerves, the branches of the X and XI cranial nerves and the nerve structures that enter them can act as targets of stimulation, which significantly expands the possibilities of neurostimulation of various processes in the brain tissue. The neck area as a “target” of neurostimulation seems to be a very interesting and promising choice.

6 DISCUSSION

Thus, as a result of experimental and fundamental studies, the main hypotheses were formulated for realizing the clinical effectiveness of the technology of multichannel neuroelectrostimulation of neural formations of the neck in the treatment of neuropsychiatric disorders.

Due to the impact on the nodes of the sympathetic trunk and the internal carotid plexus, neurogenic regulation of cerebral blood flow is performed due to a change in the tone of the cerebral vessels of various calibers: from the main arteries to the microvasculature. The leading role in this process belongs to the superior cervical stellate ganglion.

The impact of a focused field of electrical impulses in the neck spreads in the form of electrical impulses to the sublingual, glossopharyngeal and vagus nerves, rise to the corresponding nuclei of the brain stem, reaching the cerebellum, bridge and frontal cortex. Thus, deep stimulation of the mid-stem structures of the brain is performed with the release of a large number of neurotransmitters. Under such conditions, synoptic transmission and the construction of new neural and glial networks are greatly facilitated, metabolic processes both in neurons and in neuroglia are improved. The destruction of stagnant neural networks, as well as pathological determinants and systems, is facilitated.

In clinical practice, multichannel neuroelectrostimulation technology can be used not only in the treatment of diseases of the neuropsychiatric profile, but also in the treatment of vegetative-vascular dystonia, headaches of various origins, including migraine, hypertension, sensorineural hearing loss, degenerative diseases of the eye, neuropathies of various origins, hyperhidrosis syndrome, orthostatic hypotension syndrome and postural tachycardia, vestibulopathic syndrome, as well as in the rehabilitation of patients after stroke that one.

7 CONCLUSIONS

Thus, further research is needed on the technology of multichannel electrostimulation of neck neural structure by means functional neuroimaging to expand the scope of the medical devices created on its basis. The success of such tasks can be achieved through the interaction of biologists, specialists in the field of medical physics, doctors and engineers.

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