Non-invasive Multichannel Electrostimulation of Neck Nerve Structures for the Treatment of Patients with Anxiety Disorders

Timur Petrenko[1,2], Mikhail Shalyagin[2], Konstantin Retjunskiy[2],
Vladimir Kublanov[1] and Mikhail Babich[1]
[1]*Ural Federal University, Mira 19, Yekaterinburg, Russian Federation*
[2]*Ural State Medical University, Repina 3, Yekaterinburg, Russian Federation*

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Abstract: The efficiency of non-invasive multichannel neuro-electrostimulation device (‘SYMPATHOCOR-01’) for treatment of anxiety disorders against the standard antidepressant medication is presented in article. Forty patients from psychiatric clinic with diagnosed 'panic disorder' were treated and followed-up during six weeks. The Hamilton (HAM-A) and Sheehan (SPRAS) anxiety scales were used to determine changes in state of patients. Electrostimulation has helped patients quickly overcome symptoms of anxiety and better control panic attacks. There was a significant difference in the final psychometric assessment of anxiety among groups on the Hamilton (HAM-A) and Sheehan (SPRAS) scales almost twice.

1 INTRODUCTION

Anxiety disorder is one of the most common among all mental disorders. According to the data of Russian and foreign scientists panic disorder occurs in 1,5-3,0 % of the adult population, and its subthreshold forms are diagnosed among 9-10 % of adult population in the developed countries (NIMH, 2017; Schmidt et al., 2003).

Contemporary neurophysiological studies have revealed that panic disorder develops in the midst of the increasing dysfunction of the autonomic nervous system (ANS) (Stahl and Moore, 2013). In the beginning, the ANS dysfunction is permanent and subtle. Then, it intensifies and becomes a paroxysmal one, fully defining the clinical symptoms of the panic attack (Kar and Sarkar, 2016). If the dysfunction of ANS stayed for a considerable time, it would cause irreversible changes in the blood vessels walls. This, in turn increases the risk of the vascular disorders development, which could result in stroke or heart attack (Kar and Sarkar, 2016). Autonomic disorders in different countries occurs in 25-80 % of the adult population (Schmidt et al., 1999). More than half of these people have a risk of the paroxysmal anxiety disorders.

Negative impact of the panic disorder on quality of life and social adaptation defines the relevance of the search for novel treatment approaches (Schmidt et al., 1999). At the same time, the effectiveness of the medicamentous approaches stays quite low (Starcevic, 2009).

Contemporary approaches of the anxiety disorders therapy imply psychotropic medication – antidepressants. These drugs increase exchange of the serotonin and other neuromediators in structures of the central nervous system (CNS), which are responsible for the emotions. This increases the role of the inhibitor mechanisms in the conscious control of the fear and anxiety emotions (Stahl and Moore, 2013).

However, the medicamentous approach is effective only among the one third of the patients. In most cases, the life-long drug regimen is implied, which is accompanied by the numerous side effects. Essentially, the medicamentous approach is just a substitution therapy and does not treat the disorder itself (Stahl and Moore, 2013).

Combination of the medicamentous therapy with the psychotherapy allows to increase effectiveness up to 50 % (Weaver et al., 2009). However, this approach implies life-long psychotropic drug regimen and daily psychiatrist appointments. Many patients cannot afford such expenses. In 20 % the disorder can become a malignant one. In that case, the known approaches become inefficient (Stahl and Moore, 2013).

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Recently, the methods of neuro-electrostimulation for treatment of the depressive and anxiety disorders are being actively developed (White and Tavakoli, 2015). The highest effectiveness was reported for the transcranial magnetic stimulation and invasive stimulation of the vagus nerve (Sarkar and Cohen Kadosh, 2016). The anti-depressive and anti-anxiety effects are associated with the stimulation of the brainstem nucleus and midline brain structures, which, in turn leads to the massive emission of the neurotransmitters and reconstructions of the neural networks (White and Tavakoli, 2015).

In current study, we have investigated the effectiveness of the dynamic correction of activity of the sympathetic nervous system (DCASNS) approach in comparison with standard medicamentous approaches. The DCASNS approach is realized by the medical device 'SYMPATHOCOR-01' (Kublanov et al., 2014).

2 NECK NERVE STRUCTURES

Centres for regulation of the life-important functions are placed in nucleuses of the brain stem, middle brain, the bridge, and cerebellum, and also, in the vegetative nucleuses of the neuraxis and cerebrum. Many of the conducting paths of these centers are located in the neck. The neck somatic innervation is provided by the neck neuraxis nerves that forms the massive cervical interlacing on its back surface. The afferent nerve fibers pass through the neuraxis back horns and end in the sensitive nucleuses of the brain stem and reticular formation. The reticular formation participates in processing the sensors' information and, additionally, makes activating impact onto the brain-cortex. By this way, the formation controls the neuraxis activity.

This mechanism implements the tonus control of the skeletal muscles and moreover, of the human vegetative functions. The ganglia of the sympathetic stem are placed in deep muscles of the neck. These ganglia are formed by the nerve stems of the vegetative ones of the neuraxis nervous offshoots. The upper, middle, and lower (stellular) sympathetic ganglia have multiple branches that perform sympathetic innervation of glands, brain involucres, and vessels of the neck, head and vertebra. The vagus nerve is located abreast the main neck arteries. Its ganglia are placed in the brain stem and are common with the tong-pharyngeal nerve. They have wide connections with the hypothalamus, rhinal system, and reticular formation. The pair of IX and X cranial nervous branches jointly implements para-sympathetic innervation of the majority of human organs. Together with branches of vagus nerve, ones of the neck part of the sympathetic stem form several nervous interlacings in the heart region. By this, the vegetative regulation of the heart activity is implemented. The nervous formations of neck area are tightly joined with brain stem, middle brain, cerebellum, thalamus, hypothalamus, and the large brain cortex. Presence of these connections provides participation of the neck nervous formations in analysis of irritations from sensors and in regulation of the muscle tonus, vegetative and the highest integrative functions (Moore et al., 2013; Netter, 2014). Taking into account the mentioned facts, it is perspective to use the neck neuraxis nervous interlacing and the X and IX cranial nerves as a target for electro-stimulation. It will allow one to stimulate (through the afferent paths) the grey matter of the brain stem. Through the reticular formation, this action can propagate onto the thalamic structures and the cerebrum cortex. Stimulation of the neck ganglia of the sympathetic stem will permit to affect onto both the vascular tonus of the brain arteries and onto the vegetative ganglia of the neuraxis. Thus, the neuro electro-stimulation system (under developing) is completely able to modulate the vegetative processes and affect onto the sensori-motor control and cognitive functions.

3 MATERIALS AND METHODS

3.1 Multichannel Neuro-electrostimulation Device

The group of scientists and engineers from the Ural Federal University developed the portable corrector of activity of the sympathetic nervous system ('SYMPATHOCOR-01') is an electrical pulse generator that delivers the spatially-distributed field of the carefully-controlled current pulses in the neck (Kublanov, 2008).

The device is included in the register of medical equipment products of the Russian Federation (registration certificate № FCR 2007/00757) and has the Certificate of correspondence to the requirements of the regulations GOST R 50444-92.

The spatially-distributed field of the current pulses is formed between two multi-element electrodes of the device. Each multi-element electrode comprises a cluster of thirteen partial current-conducting elements. The multi-element electrodes are arranged on the neck into left and right sides. In the working state, one element of one multi-element electrode performs the role of the anode. Elements on the other side become the cathodes. If it is necessary, the arrangement can be reversed in opposite direction.

Placing the multi-element electrodes on the subject neck, the centre elements of multi-element electrodes have to be located in projections of the neck ganglia of the sympathetic nervous system (Fig. 1).

Figure 1: Scheme of the partial current-conducting elements of the multi-element electrodes location.

Note the following basic bio-tropic characteristics of the field: the current partial pulses duration τ is from 15 to 60 usec. The number of partial pulses in the period (pulse group) is 12. The frequency f of pulses group is from 5 to 150 Hz. Pulses group period is named as T_K and calculated as $T_K=1/f$. The cathode elements are switched accordingly to each given rule (for example, a pseudo-random with the clockwise or counterclockwise direction of switching, and so on). The used anode is set depending on the stimulation target. The duration of the anode connection varies from 30 seconds to several minutes and is controlled by the doctor. The current pulses amplitude can be up to 15 mA.

Elements connection timing diagram is shown in Fig. 2.

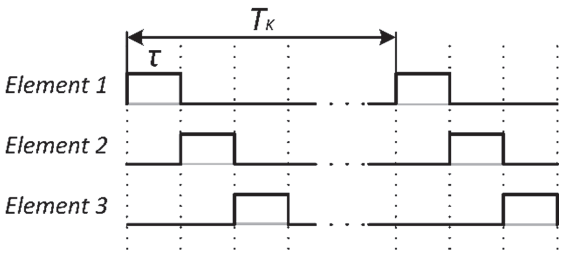

Figure 2: Elements connection timing diagram.

Before starting the stimulation, the generator connects the positive pole of the built-in current source to the element used as the anode. During stimulation process, the generator sequentially switches elements used as cathodes to the negative pole of the current source in accordance with switching order used. Cathodes and anodes connections are performed by the built-in multi-channel switches.

Depending on pathogenesis of the peripheral or central dysfunctions of the ANS, the dynamic correction of the activity sympathetic nervous system (DCASNS) algorithm has two different branches. Decision of which branch should be executed is based on nature of the ANS dysfunction. The bio-tropic parameters of the implemented current pulse field (the field structure, pulses amplitude, frequency, and duration) are calculated from the analysis of the heart rhythm variability. In particular, in the case of the abnormal hyperactivity of sympathetic innervation, it is necessary to block or suppress the activity of the sympathetic nervous system. In contrast, sympathetic innervation should be increased, if the hyperactivity of the parasympathetic innervation is observed. In case of central dysfunctions, the bio-tropic parameters of the stimulation field are calculated, based on analysis of the main activity rhythms of the cerebral cortex and its deviation from the norm.

In clinic practice, the ‘SYMPATHOCOR-01’ device and DCASNS algorithm were efficiently applied for treatment of various diseases including organic and/or functional disorders of the CNS and/or the ANS: consequences of brain trauma or stroke, epilepsy, chronic headache, somatoform disorders, anxiety and depressive spectrum disorders, attention-deficit hyperactivity disorder, disorders involving cognitive impairments (Kublanov et al., 2017).

In transistory paths of the nervous system of the neck region, there are both myelinated fiber and non-myelinated fiber. The rate of excitation propagation in the myelinated fibers is significantly larger than in the non-myelinated ones. To provide participation in stimulation of structures of various formations, it is necessary that the length of the partial spatially distributed pulses is matched with the rate of excitation propagation in the myelinated fibers, and the length of the spatially concentrated pulses' structure is matched with the rate of excitation propagation in the non- myelinated ones.

Block diagram of the engineering feasibility of multi-channel neurostimulation system is shown in Fig. 3.

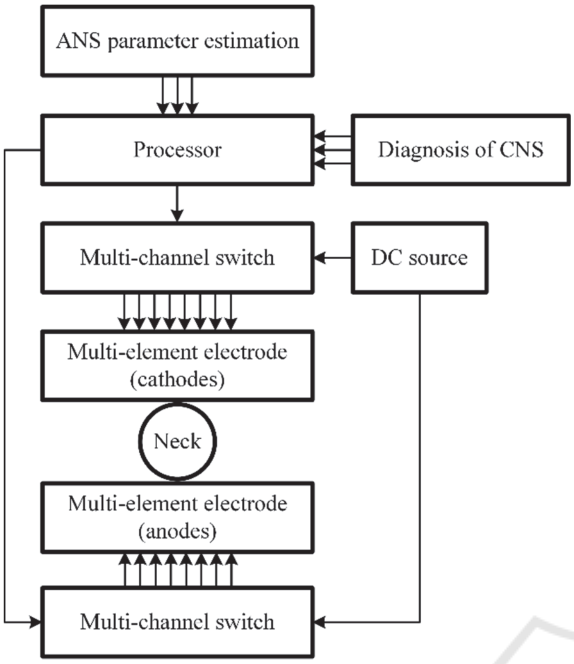

Figure 3: Block diagram of the engineering feasibility of multi-channel neurostimulation system.

The detailed technical description of the 'SYMPATHOCOR-01' device and the algorithm of the DCASNS approaches were presented in (Kublanov, et al., 2008) and (Kublanov, et al., 2017).

3.2 Clinical Data

The study on the clinical basis of the Department of Psychiatry at the State Medical University was conducted. The study has an approval of the Local Ethics committee (protocol 2 from 16.03.2007). The study included 40 outpatients with a newly diagnosed "panic disorder" ("ICD-10," 2010). All participants have signed the informed consent of participation in the study. Among the participants, there were 20 male and 20 female patients. Average age of the participants was 28,5 years. On average the disorder has lasted for 7,6 months.

The following patients were excluded from the study:

- patients, having clinically significant disease, which can prevent the therapy evaluation and which can affect safety of the therapy;
- patients, suffering from the paroxysmal anxiety within other mental disorders (bipolar disorder, schizophrenia disorder, eating disorder, obsessive-compulsive disorder, dependence on psychoactive substances);
- patients, taking psycho-pharmacological medicine prior to the study;
- female patients during pregnancy and lactation.

The period of therapy and dynamic follow-up was 6 weeks for each patient. All patients were randomly divided into two equal groups (20 patients each). In the first group (to be referred as AD), patients received drug therapy with antidepressant – escitalopram, 10 mg once daily, during whole study. In the second group (to be referred as SCR), patients were treated by means of the device 'SYMPATHOCOR-01'. The treatment course consisted of daily 15-minute long procedures, for 10 days in a row. It was allowed to take a break for a single day once during the course. After 10-day course the patients did not take any additional treatment for the rest of the study.

The medical examination was performed by the psychiatric doctor in all groups of patients initially (to be referred as T0), on the 4-th day of therapy (to be referred as T1), and then on 7-th, 10-th, 14-th, 21-st, 28-th, 35-th and 42-nd days (to be referred as T2, T3, T4, T5, T6, T7, T8 respectively). In order to evaluate effectiveness of the therapy during each visit (T0-T8) the following scales were used to estimate anxiety level and anxiety symptoms reduction degree:

- Hamilton anxiety rating scale (HAM-A) (Hamilton, 1959);
- Sheehan anxiety rating scale (SPRAS) (Schmidt et al., 2003);
- Quality-of-life index (QLI) (Katschnig, 2006);
- Global clinical impression – Severity scale (CGI-S) (Busner and Targum, 2007).

The statistical analysis was performed by the software 'STATISTICA 12'. Analysis of variance was used to find the inter-group differences.

4 RESULTS

Figures 4 – 7 show that the group of patients with neuro-electrostimulation therapy (SCR) has a faster reduction of the anxiety symptoms, evaluated by the generally accepted tests, in comparison with the antidepressant therapy group (AD).

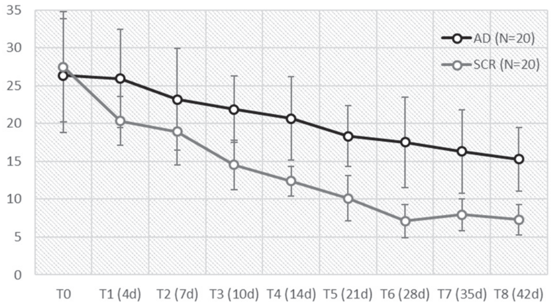

Figure 4: HAM-A dynamic for two patient’s groups.

Data on Fig. 4 shows that after 4 days of treatment the DCASNS method has a greater effectiveness than medicamentous approach. After three weeks, the anxiety evaluation for patients in second group is as for healthy people (less than 10). The DCASNS method effect stays until the end of the study.

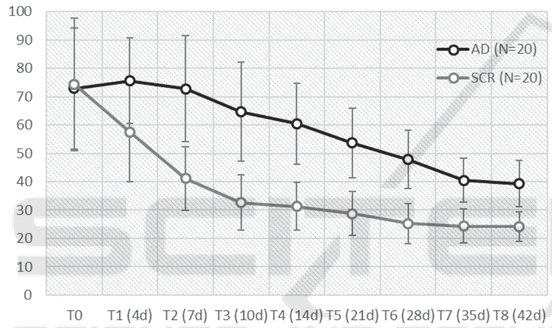

Figure 5: SPRAS dynamic for two patient’s groups.

Fig. 5 shows that after the first days the DCASNS method significantly suppresses the medicamentous treatment. After 10 days of treatment the subjective evaluation of the patients is comparable to those of healthy people (less than 40 points). It can be seen, that the effect is stable until the end of the study (day 42).

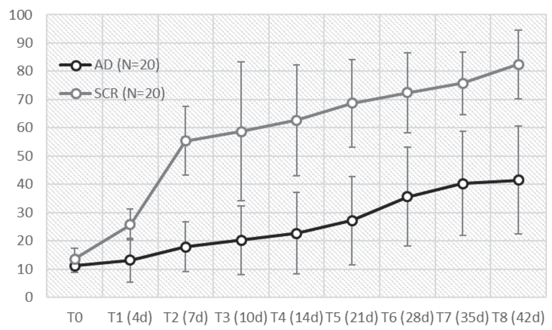

Figure 6: QLI dynamic for two patient’s groups.

Plots on Fig. 6 show that patients’ evaluation of quality of life significantly changes for two groups after the first therapy days. After first two weeks, the QLI evaluation for patients ingroup with neuro-electrostimulation therapy reaches an acceptable level (more than 60).

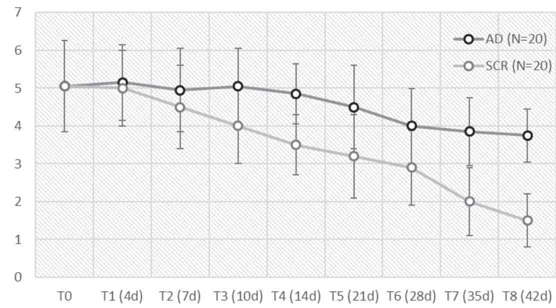

Figure 7: CGI-S dynamic for two patient’s groups.

Data on Fig. 7 shows that after 14 days of treatment the DCASNS method has a greater effectiveness than medicamentous approach. After five weeks, the global clinical impression about patients in second group is as for healthy people (less than 2).

5 CONCLUSIONS

Clinical effect of the non-invasive multi-electrode neuro-electrostimulation based on the DCASNS approach for patients with panic disorder shows high effectiveness in comparison with the medicamentous therapy. This is confirmed by the psychometric study using generally accepted scales HAM-A, SPRAS, QLI and CGI-S. The effect is most likely associated with the stimulation of the neurotransmitters emission in the stem structures of the CNS and reconstruction of the existing neural networks for most efficient functioning. This enhances the achieved clinical effect. However, this assumption needs confirmation by long-term clinical studies involving technologies of the neuroimaging. The results can be considered as a model for treating the anxiety and depression diseases.

In the future, we plan functional neuroimaging study of neuroplasticity changes after proposed neuro-electrostimulation method in patients with anxiety and depressive disorders.

Success of this technology development depends on interaction and collaboration of various specialists: engineers, physicians, physiologists, and biologists.

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