Titov I.I.
Ivano-Frankivsk National Medical University,
Ivano-Frankivsk, Ukraine

Efficacy, Safety and Tolerability of a Combination of Electrolytes with Citicoline (Neurocitin®) in Patients with Acute Ischemic Stroke: First Results of the Study

Abstract. ***Background.*** *Acute ischemic stroke is a global health problem, since most of the patients die or become disabled. In this regards, it continues to be urgent to search for new effective treatments for this pathology. We have initiated our own study to assess one of the most famous cerebroprotectors (citicoline) in combination with electrolyte (Neurocitin®) in such acute cerebral accidents.* ***Materials and methods.*** *In an open, randomized, controlled trial, it is planned to include 55 patients of both sexes aged 25 to 75 years with a diagnosis of acute ischemic stroke. The control group would consist of 25 patients with standard therapy of acute ischemic stroke by Order of the Ministry of Health of Ukraine No. 602 (without cerebroprotectors). The study group will include 30 patients with the same standard therapy + Neurocitin® 100 ml twice a day for 14 days. The primary efficacy outcomes included: the score on the NIHSS scale, Barthel index and Rankin scale by day 14 of treatment; content of neuron specific enolase (the marker of neuronal damage), the value of bispectral index (the marker of electrical activity of the cortex) by day 14 of treatment, the measure of cerebral oximetry (the marker of brain oxygenation) by day 5 of treatment; the state of cerebral hemodynamics according to Doppler ultrasound of brain vessels by discharge.* ***Results.*** *By the time of preparation of this article, both the study and control groups of the research included 20 patients each. By day 14 of treatment, the decrease of neuron specific enolase content was 2.73 times greater in the study group (with Neurocitin® (electrolyte combination of sodium, potassium, calcium and chlorine, as well as lactate and citicoline)) compared with the controls, and was close to reach normal. By day 14 of treatment, the increase of bispectral index was 64.9 % higher in the study group than in the control one, and its value practically reached normal. By day 5 of treatment, the increase of measure of cerebral oximetry was 49.6 % higher in the study group compared to the controls, and its value reached the norm. In many cases, an improvement in the group of Neurocitin® developed earlier compared to the treatment without cerebroprotector.* ***Conclusions.*** *Preliminary results of our study suggest that the inclusion of Neurocitin® (electrolyte combination of sodium, potassium, calcium and chlorine, as well as lactate and citicoline) into the scheme of treatment of acute ischemic stroke leads to a significantly more rapid reduction of neuronal damage, restore the electrical activity of the cortex and brain oxygenation compared to the therapy without cerebroprotector. In many cases, these effects are observed at an earlier date. Preliminary results of the study indicate the desirability of Neurocitin® inclusion into the current protocols of treatment for acute ischemic stroke.*

Keywords: *Neurocitin®; citicoline; acute ischemic stroke; neuron specific enolase; bispectral index; cerebral oximetry; comprehensive neuroprotection.*

For correspondence: Ivan I. Titov, MD, PhD, Professor, Ivano-Frankivsk National Medical University, 2, Halytska St., Ivano-Frankivsk, 76018, Ukraine;
E-mail: titovdoc@rambler.ru

Introduction

100-120 thousand new cases of cerebral stroke are registered in Ukraine annually, most of which are ischemic in nature. Around 50% of patients die within 1 year after a suffered stroke while the majority of survivors become disabled. Consequently, a search for ways to improve the intensive care in the stroke acute period and subsequent rehabilitation is an important medical task [1-4].

So far, many curative aspects of acute ischemic stroke have been reconsidered. In particular, the necessity to conduct a sufficient fluid therapy for maintenance of the normovolemia in the patient's body has been substantiated. Nowadays the tactic of restriction of fluid injections and conducting of dehydration is considered unacceptable. It is important to maintain the condition of normoosmolarity in the blood plasma and the normal hematocrit level. It is unacceptable to apply solutions containing glucose as hyperglycemia intensifies the acidosis in the ischemic brain regions. Furthermore, the glucose solutions are sources of free fluid which can contribute to development of cerebral edema [5, 6].

A special place among measures to provide care to patients with ischemic stroke occupies prescription of medications that improve the nerve tissues. According to P. Sahota et al., the most promising interventions ensuring neuroprotection in the acute stage of stroke and tested in large clinical trials, are hypothermia, magnesium sulfate, citicoline and albumin. However, the most promising interventions intensifying the neurorecovery in the subacute stage of stroke are granulocyte colony-stimulating factor (G-CSF), citicoline and cell therapy [7]. It is apparent that only citicoline shows a pronounced efficiency both in the acute and subacute stages of stroke, and at the same time it does not cause significant side effects [8].

Citicoline (cytidine 5'-diphosphocholine, CDP-choline) is an important intermediate in the biosynthesis of phosphaditidylcholine – a major component of biological membranes. The experimental studies of acute ischemic stroke have confirmed the citicoline's ability to decrease the amount of stroke, cerebral edema, neurologic impairment, to improve educability, memory and performance of behavioural tasks [9]. The mechanisms underlying the said curative effects are presented in Figure 1.

As opposed to experimental studies of acute ischemic stroke where mostly positive results were obtained, the data of clinical trials and also of their reviews, systematic reviews and meta-analyses are very contradictory. For example, the report of E. Warburton et al. (2011) mentions a systematic review (4 randomized controlled studies) where citicoline was prescribed during first 24 hours after development of a moderate or severe stroke. It was found that citicoline reliably increases the proportion of patients who completely recover after 3 months compared to placebo. However, no verifiable distinctions as to influence on mortality were found [10]. In the review of K. Overgard (clinical studies phases II and III, 2014) the authors reached the conclusions that citicoline is safe and can positively impact in acute ischemic stroke. Its effects are more visible in a less severe stroke in elderly patients who did not receive the recombinant tissue plasminogen activator. No other medication has any positive effects in confirmatory clinical trials and during conduct of subgroup analyses. Citicoline is the only medicinal product that regularly demonstrates a certain neuroprotective advantage in a large number of various clinical trials of stroke [11]. In the systematic review and formal meta-analysis of J.J. Secades et al. (10 randomized controlled trials, 2016) it is reported that the systematic review confirms certain advantages of citicoline when treating acute ischemic stroke. However, in a concomitant prescription with the best available therapy (the recombinant tissue plasminogen activator), the advantages of citicoline become inapparent [12]. In the meta-analysis of P.Y. Shi et. al. (7 randomized controlled trials, 2016) it was concluded that citicoline does not reduce mortality over the long term and the functional dependency on caregivers; the citicoline's efficiency can be not more than in the control group, although citicoline is characterized by a reliable safety level [13].

In order to further examine the citicoline's properties in patients with stroke, we have initiated our own "Study of efficacy, safety and tolerability of a combination of electrolytes with citicoline (Neurocitine®) in patients with acute ischemic stroke". A detailed description of its design and the first obtained outcomes are presented below. In this work we used Neurocitine®), solution for infusions manufactured by Yuria-Pharm Ltd. Code ATX B05B B04. Solutions for intravenous administration. Electrolytes in combination with other substances. Its main feature is that it contains electrolytes – sodium, potassium, calcium and chlorine as well as lactate and citicoline.

Neuroprotection:
- stabilization of cell membranes
- decrease of excitotoxicity (due to reduction of glutamate release)
- obstacle to development of apoptosis (due to decrease in activity of caspase system)
- reduction of an oxidative stress (by means of suppression of free radicals formation)

Neurorestauration:
- neurogenesis
- synaptogenesis
- neurotransmission modulation (by means of increase in NMDA-receptor content and intensification of neuromediators' synthesis (acetylcholine etc.))
- gluco-genesis
- angiogenesis
- increase in the number of circulating endothelial progenitor cells (EPCs)
- intensification in synthesis of proteins and nucleonic acids

Figure 1. Mechanisms of citicoline action in acute ischemic stroke (9, as amended)

Materials and methods

It is planned to include in this open randomized controlled study 55 patients of both sexes aged between 25 and 75 years with the diagnosis of "acute ischemic stroke". The stroke severity should correspond to minor and moderate grades in conformity with the National Institutes of Health (USA) Stroke Scale (NIHSS score ≤ 13). Furthermore, the diagnosis should be confirmed with the aid of neurovisualization methods - computer tomography (CT) or magnetic resonance imaging (MRI).

Pursuant to the clinical study protocol, all patients will be divided into two groups. The control group will comprise 25 patients who will be administered a standard therapy of acute ischemic stroke in conformity with Order No. 602 of the Ministry of Health of Ukraine (without cerebral protectants). The main group will comprise 30 patients who will be administered, in addition to the same standard therapy, Neurocitine® 100 ml twice a day during 14 days.

The investigators have selected a number of criteria allowing to determine the efficacy of the standard therapy + Neurocitine® in comparison with the standard therapy.

Under *key criteria* were included:

- score according to the NIHSS scale (stroke severity assessment), Barthel Index (assessment of activities of daily living) and Rankin Scale (assessment of the degree of disability and the functional independence) by day 14 of treatment;
- content of neuron specific enolase (NSE; a marker for neuronal damage); bispectral index value (BIS index; a marker of cortical electrical activity) by day 14 of treatment; measure of cerebral oximetry (rSO2; a marker of cerebral oxygenation) by day 5 of treatment;
- cerebral hemodynamics condition according to the data of an ultrasonic dopplerography (USDG) of cerebral vessels at the time of a discharge from the hospital.

Under *additional criteria* were included:

- values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) by day 14 of treatment;
- results of imaging procedures (CT, MRI) at the time of a discharge from the hospital.

In addition, the patients underwent laboratory studies (complete blood count, common urine analysis, biochemical blood test, including determination of a glucose level) and some other instrumental examinations (electrocardiography (ECG)) etc.

When performing a statistic analysis, the significance of differences was assessed using Student's t-test. The differences were considered significant at the confidence level $p < 0.05$. The following software was used: Microsoft Excel, http://medstatistic.ru.

Preliminary study results

At the time of the preparation of this article, the main and the control study groups comprised 20 patients each. Among the criteria for assessing efficiency of a standard therapy + Neurocitine® in comparison with the standard therapy, three criteria were calculated: content of neuron specific enolase, the bispectral index value and the measure of cerebral oximetry. Under initial conditions (day 1 of stroke development), there were no significant differences between the standard therapy group + Neurocitine® and the standard therapy group.

The dynamics of neuron specific enolase during 14 days after hospitalization due to the acute ischemic stroke is presented in Figure 2. Initially the content of neuron specific enolase was elevated on the average by a factor of 6.33 in both groups. The standard therapy reliably decreased this indicator starting from day 3 of treatment (there was no assessment on day 2). By day 14, the standard therapy reliably decreased this indicator by a factor of 1.43 in comparison with the initial level (day 1), however, the norm was not reached.

In the standard therapy group + Neurocitine®, the reliable decrease in neuron specific enolase was also observed since day 3. By day 14, a reliable decrease in this indicator by a factor of 3.9 in comparison with the initial level and a trend towards attainment of the norm were noted.

Thereby, the treatment efficacy in the standard therapy group + Neurocitine® was higher compared to the standard therapy group: the inclusion of Neurocitine® into the scheme of treatment resulted in an additional decrease of the neuron specific enolase content by day 14 of treatment by a factor of 2.73 in comparison with the treatment without neuroprotector.

The dynamics of BIS index during 14 days after hospitalization due to the acute ischemic stroke is presented in Figure 3. Initially the BIS index value was decreased per 2.07 in both groups compared to the norm. The standard therapy reliably increased this indicator starting from day 7 of treatment (on days 2, 3 and 5, the distinctions were not reliable). By day 14, the standard therapy reliably increased this indicator by 19.6% compared to the norm, however, the norm was not reached.

In the standard therapy + Neurocitine® group, the reliable increase in BIS index was observed since day 2. By day 14, a reliable increase in this indicator by 84.5% in comparison with the initial level was noted, which indicated the incremental recovery towards the norm.

Consequently, the treatment efficacy in the standard therapy + Neurocitine® group was reliably higher than in the standard therapy group: the inclusion of Neurocitine® into the scheme of treatment resulted in an additional increase of the BIS index by day 14 of treatment by 64.9% in comparison with the treatment without neuroprotector.

Dynamics of a cerebral oximetry during 5 days after hospitalization due to acute ischemic stroke is presented in Figure 4. Initially the measure of cerebral oximetry was reduced on average by a factor of 1.54 in both groups compared to norm. The standard therapy reliably increased this indicator starting from day 2 of treatment (on day 1, the distinctions were not reliable). By day 5, the standard therapy reliably increased this indicator by 18.9% compared to the initial level (day 1), however, the norm was not reached.

In the standard therapy + Neurocitine® group, the reliable increase of the measure of cerebral oximetry was observed since day 1. By day 5, a reliable increase in this indicator by 68.5% in comparison with the initial level was noted which reached the normal values.

Thus, the treatment efficacy in the standard therapy + Neurocitine® group was reliably higher in comparison with the standard therapy group: the inclusion of Neurocitine® into the treatment schedule resulted in an additional increase of the measure of cerebral oximetry by day 5 of treatment by 49.6% in comparison with the treatment without neuroprotector.

Discussion

In case of acute ischemic stroke, the neuron specific enolase is identified in saliva, blood plasma and cerebrospinal fluid as a marker of a neuronal damage. A connection with the neuronal damage evidences, in particular, availability of a positive correlation between the level of neuron specific enolase and the stroke amount [14 – 17]. Interestingly, hyperglycemia led to a significant increase of neuron specific enolase in patients with stroke compared to normoglycemia which indicates a larger neurons death under conditions of hyperglycemia [18, 19].

The completed studies demonstrated a diagnostic significance of the neuron specific enolase. This marker was reliably growing in patients with acute ischemic stroke in comparison with healthy persons from the control group, although it did not allowed to conduct a differential diagnosis of acute stroke with a transient ischemic attack, the conditions simulating stroke (brain metastasis, malignant hypertension), and a group of patients with the high risk of the stroke development (hypertension and/or diabetes mellitus) [14, 20, 21]. Furthermore, the study of the neuron specific enolase content had an important prognostic value for determination of stroke severity, of early and delayed neurobehavioral outcomes. At this, the higher marker values were connected with the worse prognosis [21-28]. The availability of a second elevation of neuron specific enolase peak evidenced a hemorrhagic transformation of an acute ischemic stroke [29]. At the same time, certain papers challenge the prognostic significance of neuron specific enolase [30, 31] and its correlation with the stroke volume [31].

In our study, the development of an acute ischemic stroke was associated with elevation of the neuron specific enolase content by a factor of 6.33 in comparison with the norm which indicates a sensitivity of this marker to development of an acute cerebral accident. The standard therapy and the standard therapy + Neurocitine® have reliably decreased this indicator at all study time points starting from the earliest timeframes (since day 3 of treatment; on day 2, no measurements were conducted). However, in the group with a cerebroprotector, this decrease occurred at each time point reliably faster. By day 14 of treatment, decrease in neuron specific enolase content was by factor 2.73 higher in the group with Neurocitine®, and only slightly missed the norm. The data obtained testify to the fact that inclusion of Neurocitine® into the scheme of treatment of acute ischemic stroke makes a significant additional contribution to decrease of neuronal damage.

The next indicator examined in this study, was BIS index. It is obtained by means of a complex mathematical processing of electroencephalography findings [32]. The BIS index reflects the electrical activity of the cortex [33] and is widely used in anesthesiology so that to ensure the adequate level of narcosis: not too deep or too superficial [34]. Investigation of BIS index in ischemic brain disorders is the subject of several pilot studies. In particular, in patients with acute ischemic stroke who

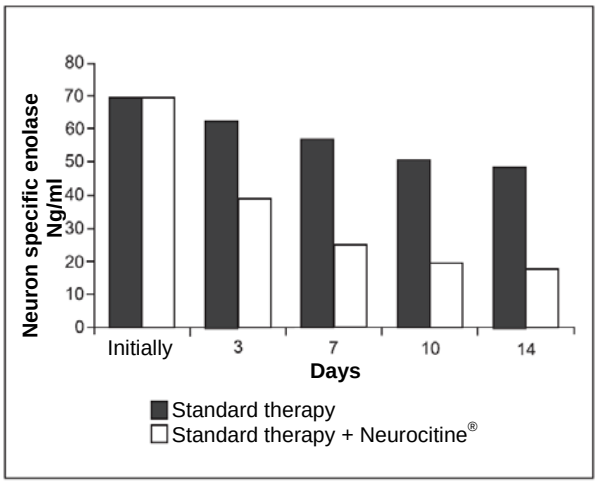

Figure 2. Dynamics of neuron specific enolase content in patients after an acute ischemic stroke during 14 days of a standard therapy in accordance with Order of the Ministry of Health of Ukraine No. 602 (without cere¬broprotectors) or a standard therapy + Neurocitine®. At all time points (days 3, 7, 10 and 14) both therapy types reliably decreased neuron specific enolase in comparison with the initial level ($p < 0.05$). At this, in all cases (days 3, 7, 10 and 14) the standard therapy + Neurocitine® was reliably more efficient than the standard therapy ($p < 0.05$). The normal content of neuron specific enolase in healthy persons amounts to ≤ 10.97 ng/ml

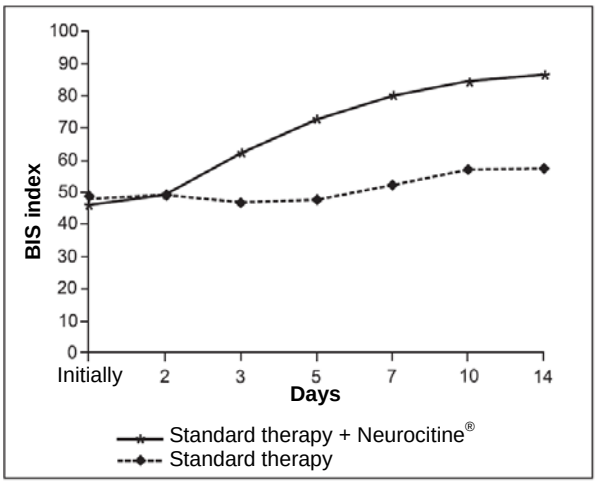

Figure 3. Dynamics of BIS index in patients after acute ischemic stroke during 14 days of a standard therapy in accordance with Order of the Ministry of Health of Ukraine No. 602 (without cerebroprotectors) or a standard therapy + Neurocitine®. The standard therapy on days 7, 10 and 14 and the standard therapy + Neurocitine® on days 2, 3, 5, 7, 10, 14 reliably increased BIS index in comparison with the initial level ($p < 0.05$). At this, on days 3, 5, 7, 10 and 14 the standard therapy + Neurocitine® was reliably more efficient than the standard therapy ($p < 0.05$). The normal value of BIS index in healthy persons amounts to ≥ 98

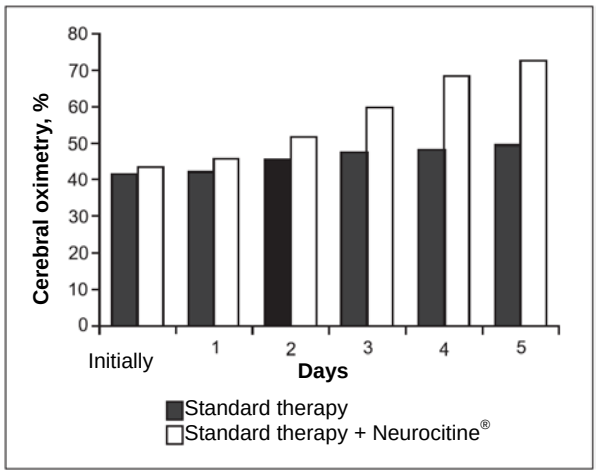

Figure 4. Dynamics of the measure of cerebral oximetry in patients after acute ischemic stroke during 5 days of a standard therapy in accordance with Order of the Ministry of Health of Ukraine No. 602 (without cere¬broprotectors) or a standard therapy + Neurocitine®. The standard therapy on days 2, 3, 4, 5 and the standard therapy + Neurocitine® on days 1, 2, 3, 4, 5 reliably increased the measure of cerebral oximetry in comparison with the initial level (p < 0.05). At this, on days 1, 2, 3, 4, 5 the standard therapy + Neurocitine® was reliably more efficient than the standard therapy (p < 0,05). The normal measure of cerebral oximetry in healthy persons amounts to ≥ 65%

underwent a recanalization, BIS index correlated well with clinical and radiological data. An elevation of BIS index was a powerful independent predictor of a clinical response after recanalization [35]. Another paper describes a pati ent who developed a transient ischemic attack of the cerebral trunk immediately before the forthcoming cardiac surgery. The BIS index value dropped to 60, and when consciousness spontaneously recovered, it increased up to 85. The authors consider that lack of incoming influences from the brain stem to the frontal cortex led to decrease in cortical electrical activity which affected the BIS index value [20]. Two studies reported on sensitivity of BIS index to development of stroke in a patient with the artificial blood-circulation apparatus [36] and one more patient with perioperative stroke [37].

In our study, development of acute ischemic stroke was connected with a decrease in a BIS index value by a factor of 2.07 in comparison with the norm which indicates sensitivity of this marker to development of an acute cerebral accident. The standard therapy + Neurocitine® increased this indicator earlier (starting from day 2) compared to the standard therapy (starting from day 7) and at each time point did it reliably faster. By day 14 of treatment, the growth of BIS index was by 64.9% higher in the group with Neurocitine® and its value missed the norm only slightly. The data obtained shows that inclusion of Neurocitine® into the scheme of treatment of acute ischemic stroke makes an additional significant contribution to the restoration of the cortical electrical activity.

The measure of cerebral oximetry (rSO2) defines a regional oxygen saturation of cerebral tissue. The technique is non-invasive, the assessed blood is arteriovenous (mixed) [38, 39]. The cerebral oximetry can be used for evaluation of the cerebral oxygenation during various phases of ischemic stroke. It allows to reveal a decrease in cerebral oxygenation, estimate the efficacy of ongoing treatment and carry out subsequent patient monitoring [40, 41]. It is also applied in strokes at an early age [42]. The cerebral oximetry helped to manage neuroanesthesia and prognosticate the outcome after an endovascular therapy for acute ischemic stroke [43]. This technique allowed to reduce the risk of stroke development during cardiac surgery since it made it possible to timely correct oxygen delivery to the brain [44, 45] although in one publication a similar role of a cerebral oximetry in cardiac surgery was called in question [46]. The cerebral oximetry helped to prevent stroke development also in other operative interventions such as a *carotid endarterectomy [47-49] and liver transplantation [50], and also in patients on hemodialysis due to chronic kidney diseases [51]*.

In our study the development of acute ischemic stroke was connected with decrease in the measure of cerebral oximetry by a factor of 1.54 in comparison with the norm which indicates a sensitivity of this marker to development of an acute cerebral accident. The standard therapy + Neurocitine® increased this indicator at an earlier date (since day 1) and did it at all time points reliably faster. By day 5 of treatment, the growth of the measure of cerebral oximetry was by 49.6% greater in the group with Neurocitine® and its magnitude reached normal values. The data obtained testify to the fact that inclusion of Neurocitine® into the scheme of treatment of an acute ischemic stroke makes a significant additional contribution to the restoration of brain oxygenation.

Conclusions

Acute ischemic stroke is one of the most pressing problems of modern medicine as its development is associated with a significant mortality and disablement of patients. Therefore, the task of optimizing the existing therapy and searching for new approaches to increase its efficacy continues to be relevant. Preliminary results of our study testify the fact that inclusion of Neurocitine® into the scheme of treatment of acute ischemic stroke leads to a reliably faster decrease in neuronal damage, restoration of electrical activity of the cortex and oxygenation of the brain compared to the therapy without a neuroprotector. At this, Neurocitine® in many cases triggers these improvements at an earlier date after development of acute ischemic stroke in comparison with the therapy without a neuroprotector.

Due to the fact that Neurocitine® accelerates recovery of patients after acute ischemic stroke due to faster normalization of indicators and an earlier effect, it seems reasonable to include this medicinal product into the protocols of treatment of this type of acute brain accidents. However, the described preliminary results should be once more re-evaluated after the fully completion of the study.

Conflict of interest. Not reported.

Reference

1. Mishchenko T.S. Treatment of patients with ischemic stroke// Health of Ukraine. — 2015. — http://health-ua.com

2. Chief officer of MoH of Ukraine on prevention and treatment of cerebral strokes//http://medinfo.ua

3. Stroke Academy — 2015: time to act! // Health of Ukraine. — 2015 (thematic issue). — P. 14-16.

4. Thrombolysis in ischemic stroke — recanalization, neuroprotection and subsequent *carotid endarterectomy* / Yevtushenko S.K., Shchepotynnyk E.V., Rodin Yu.V., Dyuba D.Sh.// The Journal of Neuroscience of B.M. Mankovsky. — 2013. — V. 1, No. 2. — P. 69-72.

5. Titov I.I. Key issues of intensive care in patients with acute cerebral accidents // III International congress on infusion therapy — 2016. — https://www.youtube.com/ watch?v = ex274I1TXJU

6. Order of MoH of Ukraine dated 03.08.2012 No. 602 "On approval and introduction of medicinal and technological documents on standardization of medical assistance in ischemic stroke" // http://www.moz.gov.ua

7. Sahota P., Savitz S.I. Investigational Therapies for Ischemic Stroke: Neuroprotection and Neurorecovery // Neurotherapeutics. — 2011. — V. 8, № 3. — P. 434-451.

8. Secades J.J., Lorenzo J.L. Citicoline: pharmacological and clinical review, 2006 update // Methods Find. Exp. Clin. Pharmacol. - 2006. - V. 28 (Suppl. B). - P. 1-56.

9. Alvarez-Sabin J., Roman G.C. The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke // Brain Sciences. - 2013. - V. 3, № 3. - P. 1395-1414.

10. Stroke management / Warburton E., Alawneh J.A., Clat- worthy PL., Morris R.S. // BMJ Clin. Evid. - 2011. - V. 2011, pii: 0201.

11. Overgaard K. The effects of citicoline on acute ischemic stroke: a review // J. Stroke Cerebrovasc. Dis. — 2014. — V. 23, № 7. - P. 1764-1769.

12. Citicoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-Blind, and Placebo-Controlled Trials / Secades J.J., Alvarez-Sabin J., Castillo J. et al. //J. Stroke Cerebrovasc. Dis. — 2016. — *V* 25, № 8. — P. 1984-1996.

13. Early application of citicoline in the treatment of acute stroke: A meta-analysis of randomized controlled trials /Shi P.Y., Zhou X.C., Yin X.X. et al. // J. Huazhong Univ. Sci. Technolog. Med. Sci. — 2016. - V. 36, № 2. - P. 270-277.

14. Al-Rawi N.H., Atiyah K.M. Salivary neuron specific enolase: an indicator for neuronal damage in patients with ischemic stroke and stroke-prone patients // Clin. Chem. Lab. Med. — 2009. — V. 47, № 12. - P. 1519-1524.

15. Neuron-specific enolase and tau protein as neurobiochemical markers of neuronal damage are related to early clinical course and long-term outcome in acute ischemic stroke / Wunderlich M.T., Lins H., Skalej M. et al. // Clin. Neurol. Neurosurg. — 2006. —108, № 6. - P. 558-563.

16. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke / Missler U., Wiesmann M., Friedrich C., Kaps M. // Stroke. - 1997. - *V* 28, № 10. - P. 1956-1960.

17. Li Y., Wang X., Yang Z. Neuron-specific enolase in patients with acute ischemic stroke and related dementia // Chin. Med. J. (Engl). - 1995. - V. 108, № 3. - P. 221-223.

18. Sulter G., Elting J.W., De Keyser J. Increased serum neuron specific enolase concentrations in patients with hyperglycemic cortical ischemic stroke // Neurosci. Lett. — 1998. — V. 253, № 1. — P. 71-73.

19. Correlative study between neuron-specific enolase and blood sugar level in ischemic stroke patients / Pandey A., Saxena K., Verma M., Bharosay A. // J. Neurosci. Rural. Pract. — 2011. —

V 2, № 1. - P. 50-54.

20. Serum neuron-specific enolase and S100 calcium binding protein B biomarker levels do not improve diagnosis of acute stroke / González-García S., González-Quevedo A., Peña-Sánchez M. et al. // J. R.. Coll. Physicians Edinb. - 2012. - V. 42, № 3. - P. 199-204.

21. Serum neuron-specific enolase, carnosinase, and their ratio in acute stroke. An enzymatic test for predicting outcome? / Butterworth R.J., Wassif W.S., Sherwood R.A. et al. //Stroke. — 1996. — 27, № 11. - P. 2064-2068.

22. Pandey A., Shrivastava A.K., Saxena K. Neuron specific enolase and c-reactive protein levels in stroke and its subtypes: correlation with degree of disability //Neurochem. Res. — 2014. — V. 39, № 8. - P. 1426-1432.

23. Prognostic value of neuron specific enolase and IL-10 in ischemic stroke and its correlation with degree of neurological deficit / Singh H.V., Pandey A., Shrivastava A.K. et al. // Clin. Chim. Acta. - 2013. - *V* 419. - P. 136-138.

24. Short-term prognostic value of serum neuron specific enolase and S100B in acute stroke patients / González-García S., González- Quevedo A., Fernández-Concepción O. et al. // Clin. Biochem. — 2012. - *V* 45, № 16-17. - P. 1302-1307.

25. Islam N., Ullah E., Akhtar N. Correlation between serum neuron specific enolase and functional neurological outcome in patients of acute ischemic stroke / Zaheer S., Beg M., Rizvi I. et al. // Annals of Indian Academy of Neurology. — 2013. — V. 16, *№* 4. — P. 504-508.

26. Correlation of Brain Biomarker Neuron Specific Enolase (NSE) with Degree of Disability and Neurological Worsening in Cerebrovascular Stroke / Bharosay A., Bharosay V.V., Varma M. et al. // Indian J. Clin. Biochem. — 2012. — V. 27, № 2. — P. 186-190.

27. Prognostic value of somatosensory evoked potentials, neuron- specific enolase, and S100 for short-term outcome in ischemic stroke/ Haupt W.F., Chopan G., Sobesky J. et al. // J. Neurophysiol. — 2016. - V. 115, № 3. - P. 1273-1278.

28. Temporal profile and clinical significance of serum neuron-specific enolase and S100 in ischemic and hemorrhagic stroke / Brea D., Sobrino T., Blanco M. et al. // Clin. Chem. Lab. Med. — 2009. - V. 47, № 12. - P. 1513-1518.

29. The second elevation of neuron-specific enolase peak after ischemic stroke is associated with hemorrhagic transformation / Kim B.J., Kim Y.J., Ahn S.H. et al. // J. Stroke Cerebrovasc. Dis. —

2014. - V. 23, № 9. - P. 2437-2443.

30. Anand N. Stead L.G. Neuron-specific enolase as a marker for acute ischemic stroke: a systematic review// Cerebrovasc. Dis. — 2005. - V. 20, № 4. - P. 213-219.

31. Kaca-Oryńska M., Tomasiuk R., Friedman A. Neuron-specific enolase and S 100B protein as predictors of outcome in ischaemic stroke // Neurol. Neurochir. Pol. — 2010. — V. 44, № 5. - P. 459-463.

32. Myles P.S. Bispectral index monitoring in ischemic-hypoxic brain injury// J. Extra. Corpor. Technol. — 2009. — V. 41, *№* 1. — P. 15-19.

33. Bispectral Index Changes during Acute Brainstem TIA/ Ischemia/Bleeker C.P., Smits B., Vos P.E., Mourisse J.M. // Case Rep. Med. - 2010. - V. 2010, Article ID 697185.

34. Bigham C., Bigham S., Jones C. Does the bispectral index monitor have a role in intensive care? // J. Intensive Care Soc. - 2012. - 13. - 314-9.

35. Monitoring of cortical activity postreperfusion. A powerful tool for predicting clinical response immediately after recanalization /Flores A.1, Ribo M., Rubiera M. et al. // J. Neuroimaging. —- V. 25, № 2. - P. 257-262.

36. Leggat C.S., Fischer G.W. Early detection of an acute cerebral event during cardiopulmonary bypass using a bispectral index monitor// Semin. Cardiothorac. Vasc. Anesth. — 2008. — V. 12, № 1. - P. 80-82.

37. The bispectral index in the diagnosis of perioperative stroke: a case report and discussion / Welsby I.J., Ryan J.M., Booth J.V. et al. // Anesth. Analg. - 2003. - V. 96, № 2. - P. 435-437.

38. Murkin J.M., Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation // Br. J. Anaesth. — 2009.— V. 103. (Suppl. 1) — P.i3-i13.

39. Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain- injured patients/ Taussky P., O'Neal B, Daugherty W.P. et al. // Neurosurg. Focus. - 2012. - V. 32, № 2. - P. E2.

40. The evaluation of cerebral oxygenation by oximetry in patients with ischaemic stroke / Demet G, Talip A., Nevzat U. et al. // J. Postgrad. Med. - 2000. - V. 46, № 2. - P. 70-74.

41. Brain oxygen supply in the residual period of ischemic stroke/ Kamenskaia O.V., Levicheva E.N., Loginova I.Iu, Karpenko A.A. // Zh. Nevrol. Psikhiatr. Im. S.S. Korsakova. - 2012. - V. 112, № 8 (Pt. 2). - P. 20-24.

42. Cerebral oximetry with cerebral blood volume index in detecting pediatric stroke in a pediatric ED / Abramo T.J., Harris Z.L, Meredith M. et al. //Am. J. Emerg. Med. - 2015. - V. 33, № 11. - P. 1622-1629.

43. Noninvasive cerebral oximetry during endovascular therapy for acute ischemic stroke: an observational study / Hametner C., Stanarcevic P., Stampfl S. et al. // J. Cereb. Blood Flow Metab. — 2015. - V. 35, № 11. - P. 1722-1728.

44. Outcome improvement and cost reduction in an increasingly morbid cardiac surgery population / Goldman S.M., Sutter F.P., Wertan M.A. et al. //Semin. Cardiothorac. Vasc. Anesth. — 2006. — V. 10, № 2. - P. 171-175.

45. Murkin J.M. Is it better to shine a light, or rather to curse the darkness? Cerebral near-infrared spectroscopy and cardiac surgery // Eur. J. Cardiothorac. Surg.. - 2013. - V. 43, № 6. - P. 1081-108

46. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review / Zheng F., Sheinberg R., Yee M.S. et al.//Anesth. Analg. — 2013. —116, № 3. — P. 663-676.

47. Cerebral monitoring in patients undergoing carotid endarterectomy using a triple assessment technique / Ali A.M., Green D., Zayed H. et al. // Interact. Cardiovasc. Thorac. Surg. — 2011. —

V *12, № 3. — P. 454-457.*

48. The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review / Pennekamp C.W., Bots M.L., Kappelle L.J. et al. // Eur. J. Vasc. Endovasc. Surg. — 2009. — V. 38, № 5. — P. 539-545.

49. Cerebral oximetry monitoring during carotid endarterectomy: effect of carotid clamping and shunting/ Cuadra S.A., Zwerling J.S., Feuerman M. et al. //Vasc. Endovascular. Surg. — 2003. — V. 37, № 6. — P. 407-413.

50. Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation / Zheng Y., Villamayor A.J., Merritt W. et al. // Neurocrit. Care. — 2012. — V. 17, № 1. — P. 77-84.

51. Cerebrovascular effects of hemodialysis in chronic kidney disease / Prohovnik I., Post J., Uribarri J. et al. // J. Cereb. Blood Flow Metab. — 2007. — V. 27, № 11. — V. 1861-1869.

Received on 09.02.2014 ■

I.I. Titov
Ivano-Frankovsk National Medical University, Ivano-Frankovsk, Ukraine

Efficacy, Safety and Tolerability of a Combination of Electrolyte with Citicoline (Neurocitin®) in Patients with Acute Ischemic Stroke: First Results of the Study

Abstract. ***Background.*** Acute ischemic stroke is a global medical problem, since most of the patients die or become disabled. In this regard, it continues to be urgent to search for new effective treatments for this pathology. We have initiated our own study to assess one of the most famous cerebroprotectors (citicoline) in combination with electrolyte (Neurocitin®) in such acute cerebral accidents. ***Materials and methods.*** In an open, randomized, controlled trial, it is planned to include 55 patients of both sexes aged 25 to 75 years with a diagnosis of acute ischemic stroke. The control group would consist of 25 patients with standard therapy of acute ischemic stroke by Order of the Ministry of Health of Ukraine No. 602 (without cerebroprotectors). Study group will include 30 patients with the same standard therapy + Neurocitin® 100 ml 2 times a day for 14 days. The primary efficacy outcomes included: the score on the NIHSS scale, Barthel index and Rankin scale by day 14 of treatment; content of neuron specific enolase (the marker of neuronal damage), the value of bispectral index (the

marker of electrical activity of the cortex) by day 14 of treatment, the measure of cerebral oximetry (the marker of brain oxygenation) by day 5 of treatment; the state of cerebral hemodynamics according to Doppler ultrasound of brain vessels by discharge. ***Results.*** By the time of preparation of this article, both the study and control groups of the research included 20 patients each. By day 14 of treatment, the decrease of neuron specific enolase content was 2.73 times greater in the study group (with Neurocitin® (electrolyte combination of sodium, potassium, calcium and chlorine, as well as lactate and citicoline)) compared with the controls, and was close to reach normal. By day 14 of treatment, the increase of bispectral index was 64.9 % higher in the study group than in the control one, and its value practically reached normal. By day 5 of treatment, the increase of measure of cerebral oximetry was 49.6 % higher in the study group compared to the controls, and its value reached the norm. In many cases, an improvement in the group of Neurocitin® developed earlier compared to the treatment without cerebroprotector. ***Conclusions.*** Preliminary results of our study suggest that the inclusion of Neurocitin® (electrolyte combination of sodium, potassium, calcium and chlorine, as well as lactate and citicoline) into the scheme of treatment of acute ischemic stroke leads to a significantly more rapid reduction of neuronal damage, restoration of the electrical activity of the cortex and brain oxygenation compared to the therapy without cerebroprotector. In many cases, these effects are observed at an earlier date. Preliminary results of the study indicate the desirability of Neurocitin® inclusion into the current protocols of treatment for acute ischemic stroke.
Keywords: Neurocitin®; citicoline; acute ischemic stroke; neuron specific enolase; bispectral index; cerebral oximetry; comprehensive neuroprotection.