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Research Article

REVIEW OF CITICOLINE APPLICATION IN THE COMPLEX TREATMENT AND REHABILITATION OF PATIENTS WITH ACUTE ISCHEMIC STROKE

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ABSTRACT

The review is devoted to the citicoline application in the complex treatment and rehabilitation of patients with acute ischemic stroke. The results of numerous experimental and clinical studies of the effect of citicoline on ischemia and hypoxia of the brain are presented. The basic pharmacological properties of citicoline, which has a complex neuroprotective effect are highlighted. Data are presented on the latest multicenter placebo-controlled trials of the drug in acute stroke. The basic principles of successful neurorehabilitation in stroke are discussed: early onset, continuity, continuity, multidisciplinary organizational approach, combination of rehabilitation measures and medication support of neuroplasticity [4,6].

KEYWORDS

Ischaemic stroke, neuroprotection, reparative therapy, citicoline, rehabilitation.

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INTRODUCTION

The improvement of care during post-stroke rehabilitation is one of the most actual scientific and practical problems of modern medicine. Stroke results in permanent disability of patients, significant decrease of social and everyday functioning. From the viewpoint of general pathophysiology, alterations in the nervous system at stroke include two kinds of phenomena: damage of morphological structures with violation of functional connections, and the appearance of new integrations pathological in nature and results of activity - pathological systems[7,18].

The strategy of rehabilitation therapy is to eliminate or reduce the activity of pathological systems that serve as the pathophysiological basis for the formation of persistent neurological syndromes . According to G.N. Kryzhanovskii [2], this goal can be achieved by suppression of pathological determinants, destabilization of the pathological system, and activation of antisystems. The mechanism of disturbed functions recovery is "uninhibition" of functionally inactive nerve elements, including edema disappearance, neurons metabolism improvement, and synapses activity restoration with blood flow normalization. Another mechanism of recovery is compensation, which is provided by plasticity of brain tissue with formation of previously inactive pathways and formation of new synaptic connections [3].

Epidemiological data suggest that the incidence of motor impairment after stroke ranges from 30 to 80% (1). One of the leading problems leading to disability due to focal damage to the central nervous system is the formation of spastic paresis. Spastic paresis combines the inability to make full active movements with soft tissue shortening and muscle hyperactivity. In stroke, disorders accompanying central paresis (spasticity, contractures, pain syndrome) are usually formed by week 3-4 of the disease [4], which determines the need for early application of methods to prevent their development, i.e. rehabilitation treatment should be started before stable pathological states and systems are formed. Achievements of modern neurology in the field of diagnostics and treatment of acute violations of cerebral circulation, realized in medical practice in the form of a system of rapid

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staged care of patients with stroke, make it possible to improve significantly the outcomes of the disease. The world experience shows, that the most effective organization of the care of patients with stroke is the combination of a unit of intensive care, a unit of rehabilitation and medication support of neuroplasticity [5,16].

The system of medical care for stroke patients should necessarily include 3 stages of medical rehabilitation, starting with intensive care units, neurological departments, rehabilitation beds of hospitals, and continuing with the whole complex of therapeutic measures at the outpatient-polyclinic stage, based on multi- and interdisciplinary approaches over a long period of time. The basic principles of successful neurorehabilitation are: early onset, continuity, continuity in all phases, and a multidisciplinary organizational approach. In the acute phase of the disease, medication therapy must be continued in a staged and continuous manner from the intensive care unit. Already in the intensive care unit, the following can be initiated: positional therapy, breathing exercises, assessment and correction of swallowing disorders, passive and passive-active exercises as well as the initial stages of verticalization of patients [7,11].

Early rehabilitation is carried out to its fullest extent in specialised wards, where patients are transferred from the intensive care unit. The basis of early motor rehabilitation is ontogenetic kinesotherapy, which is designed to simulate the physiological hierarchical control of motor functions by the nervous system. It is based on reproducing in its methods the sequence of formation of the child's movements, and the use of physiological synergies in teaching everyday skills. All this allows the patient to go through the ontogenetic process of motor formation all over again [8,12].

For the recovery and training of complex motor acts (walking, balance) and fine motor skills of the hand, methods of functional biocontrol and robotic mechanotherapy based on the principle of biofeedback are used. It should be noted that throughout the treatment with the kinesotherapy and physical therapy methods, it is necessary to monitor changes in the functional state of the patient and his reaction to the proposed physical activities [9].

Rehabilitation strategies used by professionals involved in the medical rehabilitation of patients with central paresis should include medications and rehabilitation techniques that stand out

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among the large number of currently available treatments with a high degree of proven efficacy and safety [10].

The AVERT (A Very Early Rehabilitation Trial for Stroke, 2006) multicentre, evidence-based study found that the earliest rehabilitation (within the first 14 days of stroke) reduces disability, reduces mortality in the first 3 months of stroke, reduces dependence on others, reduces the frequency and severity of complications and adverse events, and improves quality of life by the end of the first year after the stroke. Regenerative and reparative therapy with drugs possessing neurotrophic and modulatory properties, improving plasticity of nervous tissue, formation of new associative connections, normalizing metabolic processes in peripheral and central nervous system is of great importance for acceleration of recovery of the broken functions.

Pathogenetic effect on the key links of the processes of repair of nerve cells has a drug citicoline, the effectiveness of which has been proved by numerous experimental and clinical studies and publications [5-10]. Because of its pharmacological properties and clinical capabilities citicoline is a unique neuroprotective drug used in the treatment of diseases accompanied by neuronal damage of [1,3]

serves as a choline donor for acetylcholine synthesis. The drug is an essential precursor of phosphatidylcholine (lecithin), the main structural component of all cell membranes, including neuronal membranes. Membrane stabilising effect of the drug is one of the main ones in cerebral ischaemia. Citicoline also inhibits the synthesis of phospholipase A2, reducing the accumulation of free fatty acids, restores the functioning of № + / K +-adenosine triphosphatase, increases the activity of antioxidant systems, prevents the processes of oxidative stress and apoptosis, a positive effect on the cholinergic transmission, modulates dopamine and glutamatergic neurotransmission. In addition, citicoline has a pronounced neuroreparative effect, stimulating the processes of neuro- and angiogenesis [15].

The pharmacological properties of citicoline have been investigated for more than 40 years. After administration, citicoline rapidly penetrates into tissues and is actively involved in metabolism, widely distributed in the cerebral cortex, white matter, subcortical nuclei, cerebellum, becoming part of the structural phospholipids of

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cytoplasmic and mitochondrial membranes [12]. The drug is practically nontoxic, and no teratogenic properties were detected.

Studies in models of ischemia found that citicoline significantly increases the concentration of adeno-zintriphosphate in the brain of both control animals and animals with ischemia, and the increase in adeno-zintriphosphate correlates with a positive effect of the drug on glutamate transport, thus having an antiexythotoxic effect [11, 16, 17]. A number of studies have demonstrated that citicoline suppresses apoptosis processes by reducing the expression of procaspases and acting on other mechanisms of antiapoptotic defense [18]. It has been shown that citicoline significantly increases the concentration of dopamine in the striatum and has a neuroprotective effect on substantia nigra [9]

Motor disturbances are a key manifestation of impaired cerebral circulation. Numerous studies have shown an acceleration of motor function recovery when using citicoline. The effect of citicoline on neuroplasticity after experimental stroke has been shown to contribute to the recovery of motor and cognitive skills in animals [16, 17]. In the 1st double-blind, multicentre placebo-controlled study in 1988, it was demonstrated that citicoline was effective for the treatment of acute stroke and produced fewer complications than placebo [2]. Similar results were also obtained later in other research centres .A large study including 899 patients on the effectiveness of oral citicoline in ischemic stroke was conducted in the USA (ESSO, 2000) [13]. Patients took citicoline at a dose of 2 g/day for 6 weeks. In the citicoline group, compared with the placebo group, there was a trend towards good recovery of motor neurological function and a reduction in lesion volume, which correlated significantly with clinical improvement .

Numerous studies have shown that when using citicoline in the acute period of ischaemic stroke there is a reduction in the volume of brain infarction, improved dynamics of recovery of motor function, walking and self-care. There is evidence of a positive effect of combined therapy with other neurometabolic agents.

In a study to assess the effectiveness of combined therapy with Ceraxon® (citicoline) and Actovegin® involving 104 patients aged 55-80 years in the acute period of ischemic stroke, patients were divided into 4 groups: Group 1 patients (n=25) received standard baseline

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therapy; Group 2 patients (n=25) additionally received citicoline (1000 mg/day, intravenous drip on 200 ml saline) for 10 days; Group 3 patients (n=26) additionally received Actovegin® (250 ml 20% solution intravenously drip on saline) for 10 days; Group 4 (n=28) received combined therapy of citicoline and Actovegin for 10 days. The evolution of the condition was carried out on days 2, 7, 10 and 30; brain computed tomography parameters (on day 5), neurological status, National Institute of Health (NIH) stroke scale, Rankine Scale, Barthel Index were assessed. The most pronounced effect of the administered therapy was seen in Group 4 patients treated with the combined therapy of citicoline and actovegin compared to the control group: by the 5th day the tendency to a more significant decrease of the cerebral ischemic damage in dynamics was revealed, on the 10th day there was a significant acceleration of the regression of neurological symptoms according to the NIH scale, by the 30th day there was a significantly more significant functional recovery according to Rankin scale and Barthel index. It was found out, that in the 3rd group of patients treated with citicoline, dynamics of parameters was similar to that in the 4th group (Rankin's scale and Barthel's index). Thus, the combined use of citicoline and Actovegin is the most optimal, as it leads to a more complete regression of neurological deficit and greater functional independence of the patient by the end of the acute period of stroke.

The review articles provide data on the optimal dosing regimen based on the results of clinical trials of the drug. So citicoline, administered at a dose of 1000 mg/day for 8 weeks, accelerated regression of hemiplegia, intravenous administration of the drug at a dose of 750 mg/day for 10 days, starting from the first 48 hours after the appearance of symptoms of stroke, contributed to the restoration of motor and cognitive functions, with intravenous administration of 1 g for 14 days marked by more rapid recovery of consciousness, a significant improvement in general condition and functional status. It is noted that a relatively high functional status was achieved in 61.3% of those who took citicoline at a dose of 500 mg/day, 39.4% of those who took citicoline at a dose of 1000 mg/day, and 52.3% of those who took citicoline at a dose of 2000 mg/day. The degree of improvement in the groups receiving citicoline at a dose of 500 and 2000 mg/day was approximately the same.

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The ICTUS trial (an international randomised placebo-controlled trial of the efficacy and safety of citicoline in patients with moderate to severe ischaemic stroke, 2012) in which 2298 patients with stroke by randomisation received citicoline or placebo within 24 h of symptom onset (1000 mg every 12 h intravenously for the first 3 days, then orally in 1 tablet 500 mg every 12 h) for 6 weeks. The results of the study confirmed the safety of citicoline in ischaemic stroke. Another multicentre placebo-controlled trial included 394 patients with ischaemic stroke in the middle cerebral artery basin with an NIHSS score of 5 or higher. Cithicoline was administered in the first 24 h after the onset of symptoms at a dose of 500 mg/day. On average, the first dose of citicoline was administered 12 hours after the onset of symptoms. Long-term observation showed that during citicoline administration more patients with moderate and severe stroke (NIHSS score of 8 or higher) by the end of 12 weeks had achieved a nearly complete recovery and had a Barthel index of at least 95 (33% vs 21% on placebo). In contrast, patients with mild stroke showed no significant difference to placebo due to good spontaneous recovery.

A placebo-controlled study of the efficacy and safety of citicoline in 38 patients with intracerebral haemorrhage was also carried out. Treatment was initiated within the first 6 h of symptom onset and included intravenous citicoline 1 g every 12 h for 2 weeks. Adverse events occurred with equal frequency on citicoline and placebo administration. By the end of the study, 5 patients treated with citicoline and only 1 placebo injected could be considered functionally independent (modified Rankin score less than 3). Thus, citicoline can be considered safe for intracerebral haemorrhage .

Citicoline is the only neuroprotective agent included in the 2008 European guidelines for the treatment of stroke [7].

Thus, citicoline, a drug based on a natural precursor of the main structural component of cell membranes, is a safe neuroprotective agent, the effectiveness of which has been proven in a number of neurological diseases. Me-analysis of experimental and clinical studies of citicoline showed its effectiveness in acute stroke. Based on the results of the studies, it is possible to recommend citicoline in ischemic stroke, starting from the first minutes of the disease. Given the safety of the drug in hemorrhagic stroke, it can be

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administered before neuroimaging - during transport of the patient in the ambulance. The optimal dose at this stage of treatment is 2000 mg and the optimal route of administration is intravenous infusion. Thereafter, it is reasonable to continue infusion for at least 7-14 days (depending on the severity of the patient's condition). Thereafter, either intramuscular or intravenous administration (doses may range from 500 to 1000 mg/day) may be used [5].

Given citicoline's ability to accelerate recovery of neuropsychological and motor functions, its administration may be continued for up to 6 months or longer. In the early and later stages of stroke treatment, citicoline should be combined with drugs with a different mechanism of action. In particular, in the first hours of ischaemic stroke, citicoline can be combined with thrombolysis and other neuroprotective agents (eg, Actovegin). Experience has proved that the success of rehabilitation treatment of patients with stroke depends on the correct organisation of the rehabilitation process, a combination of methods of physical and medicamental influence, based on the principles of evidence-based medicine.

REFERENCES

1. Khozhieva D.T., Pulatov S.S., Khaidarova D.K. 2015. All about hemorrhagic stroke in the elderly and elderly. Science of the young. 87-96.
2. M.M. Tanashyan, K.V. Antonova, O.V. Lagoda, M.Yu. Maximova, M.V. Glebov, A.A. Shabalina, "Qandli diabetes type 2 phonida bosh miyada қon ailanining ütkir buzilishlari" "Neurology ilmii markazi" RAMS (Moscow)Clinical Neurology, Sony 8. No 3 2014, 4-8 betlar.
3. Shmonin A.A. Modern approaches to rehabilitation of patients with stroke, 12th session, St. Petersburg 2014-2015.
4. B.N. Mankovsky, Stroke in diabetic patients, Kiev. Kiev, Journal of Practical Angiology: 2-1' 2010
5. Khaidarov Nodir Kadyrovich, Shomurodov Kahramon Erkinovich, & Kamalova Malika Ilhomovna. (2021). Microscopic Examination Of Postcapillary Cerebral Venues In Hemorrhagic Stroke. The American Journal of Medical Sciences and Pharmaceutical Research, 3(08), 69–73.
6. Khodjieva D.T., Khaydarova D.K. Diagnosis and treatment of posttraumatic epilepsy.

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Journal of Research in Health Science 1 (2) issue 2018.

7. Khodjieva D.T., Khaydarova D.K. Clinical features of vertical sight disorders in patients with parkinson's disease. Journal of Research in Health Science 1 (2) issue 2018
8. Kamalova M. I., Khaidarov N. K., Islamov Sh.E. Clinical and demographic quality of life for patients with ischemic stroke in Uzbekistan academician: An International Multidisciplinary Research Journal.
1. 9.Kamalova M. I., Islamov Sh. E., Khaydarov N.K.// morphological changes in brain vessels in ischemic stroke. Journal of Biomedicine and Practice 2020, vol. 6, issue 5, pp.280-284
9. Khaidarov Nodir Kadyrovich, Shomurodov Kahramon Erkinovich, & Kamalova Malika Ilhomovna. (2021). Microscopic Examination Of Postcapillary Cerebral Venues In Hemorrhagic Stroke. The American Journal of Medical Sciences and Pharmaceutical Research, 3(08), 69–73.
10. Jauch E.C., Saver J.L., Adams H.P., Bruno A., Connors J.J., Demaerschalk B.M., Khatri P., McMullan P.W. Jr., Qureshi A.I., Rosenfield K. Scott P.A., Summers D.R., Wang D.Z., Wintermark M., Yonas H. 2013. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 44(3):870-947. doi: 10.1161/STR.0b013e318284056a.
11. Alvarez-Sabin J, Quitana M, Santamarina E, Maisterra O. 2014. Triflusal and aspirin in secondary prevention of atherothrombotic ischemic stroke: a very long-term-follow-up. Cerebrovascular Diseases. 37: 155-234.
12. Khozhieva D.T., Pulatov S.S., Khaydarova D.K. Vse o gemorragicheskom insul'te lits pozhilogo i starcheskogo vozrasta (sobstvennye nablyudeniya) [All About Hemorrhagic Stroke in the Elderly and Senile (Own Observations)]Nauka molodykh (Eruditio Juvenium), 2015, no. 3, pp. 86-96
13. Lo AC, Guarino PD, Richards LG et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med 2010; 362: 1772-83.
14. Álvarez-Sabín J, Román GC. The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke. Brain Sci 2013; 3: 1395-414.

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
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OCLC – 1272874727 METADATA IF – 6.986
Publisher: Frontline Journals

15. Salomon JA, Wang H, Freeman MK et al. The global burden of disease study 2010. Lancet 2013;380: 2053-260.

16. Sahota P, Savitz SI. Investigational therapies for ischemic stroke: Neuroprotection and neurorecovery. Neurotherapeutics 2011; 8: 434-51.

17. Zapadnyuk BV, Kopchak OO. Features drug correction of vascular cognitive disorders in patients with discirculatory encephalopathy and metabolic. Pro Neuro 2010; 4: 77.