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Innovative Neuroprotective Interventions in The Treatment of Acute Ischemic Stroke

Khaydarova Barno Israiljanovna

Senior lecturer at the Department of Human Anatomy and OHTA, Tashkent State Medical University

Abstract. Acute ischemic stroke remains one of the leading causes of mortality and long-term disability worldwide, necessitating the development of effective neuroprotective strategies. Despite advances in reperfusion therapies such as thrombolysis and mechanical thrombectomy, neuronal injury caused by ischemia–reperfusion mechanisms continues to limit functional recovery. This article reviews innovative neuroprotective interventions aimed at reducing neuronal damage, modulating inflammatory responses, minimizing oxidative stress, and enhancing neuroplasticity. Emerging therapeutic approaches include targeted pharmacological agents, antioxidant and anti-inflammatory compounds, stem cell-based therapies, and combination treatment strategies integrated with reperfusion techniques. Additionally, the role of personalized medicine and biomarker-guided therapy is discussed as a promising direction in optimizing treatment outcomes. The integration of innovative neuroprotective interventions into standard stroke management protocols may significantly improve neurological recovery and reduce long-term disability.

Key words: Acute Ischemic Stroke, Neuroprotection, Oxidative Stress, Neuroinflammation, Reperfusion Therapy, Stem Cell Therapy, Personalized Medicine, Neuronal Recovery

Relevance.

The current "gold standard" for the treatment of ischemic stroke is reperfusion through thrombolysis. However, the use of thrombolytic therapy has a number of organizational and clinical limitations. So, according to ChangT.S. due to time constraints and side effects of thrombolysis, only about 3% of all stroke patients receive it. Neuroprotection is an alternative treatment for stroke. Experimental studies have shown that neuroprotective drugs can restore up to 80% of the volume of ischemic tissue (3). More than 80% of stroke patients permanently lose their ability to work, and only 10.2% of surviving patients return to work (1). By 2030, mortality from stroke is projected to increase worldwide to 7.8 million people per year, unless active global measures are taken to combat this epidemic (2).

Recently, a definition of neuroprotection in ischemic stroke has been developed as a treatment strategy aimed at reducing, interrupting or slowing down the sequence of biochemical or molecular processes that lead to irreversible brain damage (4). Despite the fact that the effectiveness of many drugs has been demonstrated in experimental studies, in clinical settings, cases of proven effectiveness of neuroprotective drugs are rare. This is due to the etiological, pathogenetic and clinical heterogeneity of ischemic stroke, as well as the presence of patients with concomitant diseases that aggravate the course of stroke and prevent the directed action of neuroprotective agents. Thus, the presence of arterial hypertension, diabetes mellitus, heart failure, etc., affects the structure of the blood-brain barrier, collateral blood circulation, cellular metabolism, and the neuroimmune system. Due to these and a number of other factors, drugs that are effective under experimental conditions do not confirm their effect in the clinic.

Analysis of the dynamics of the deployment of molecular and biochemical mechanisms triggered by acute focal cerebral ischemia has established a clear time sequence of their "activation". During the first 3 hours from the moment of acute cerebrovascular accident, the maximum energy deficit in the ischemic tissue is presented; after 3-6 hours - glutamate-calcium excitotoxicity and lactic acidosis, fading away by the end of the 1st day [5].

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Such consequences of ischemia as oxidative stress, local inflammation, secondary microcirculatory disorders in the focus of ischemia, increased permeability of the blood-brain barrier, autoimmune reactions begin to manifest themselves in 2-3 hours, reaching a maximum in 12-36 hours. The process of apoptosis is maximally pronounced by 2-3 days. The consequences of ischemia persist for a long time - for several months, contributing to the progression of dystrophic processes and the development of encephalopathy in the post-stroke period [6].

Each step of the ischemic cascade is a potential target for therapeutic interventions. The earlier the cascade is interrupted, the greater the effect can be expected from treatment [7]. Currently, there are several goals in the fight for the survival of brain cells [9]: a decrease in glutamate expression, normalization of ion channels, restoration of phosphatidylcholine levels, and a decrease in the level of arachidonic acid and other inflammatory mediators.

A variety of mechanisms for the formation of cerebral infarction makes it possible to fairly conditionally distinguish two main directions of neuroprotective therapy: primary and secondary neuroprotection [8].

Primary neuroprotection is aimed at interrupting the rapid mechanisms of necrotic cell death - reactions of the glutamate-calcium cascade; it should be applied from the first minutes of ischemia and continue during the first 3 days of stroke [12]. Secondary neuroprotection is aimed at reducing the severity of the long-term consequences of ischemia, it can be started 3-6 hours after the development of a stroke and continue for at least a week [11]. It is proposed to use magnesium sulfate and glycine as primary neuroprotectors, methionyl-glutamyl-histidyl-phenylalanine-prolyl-glycyl-proline, ethylmethylhydroxypyridine succinate, cytoflavin as secondary ones [13].

Subsequent treatment should be aimed at activating regenerative processes. The neuroprotective effects of drugs are manifested in an increase in the resistance of brain cells to hypoxia and ischemia; correcting the level of cellular energy; improving blood supply to the brain; increasing the functional activity of neurons and glial cells; normalization of mediator imbalance [4].

Some drugs, positioned by their manufacturers as neuroprotective, in large-scale and well-designed studies have not demonstrated convincing advantages: nimodipine, magnesium sulfate, citicoline, piracetam, and many others [5]. Nevertheless, in the CIS countries, drugs with neuroprotective properties are widely used in the treatment of ischemic stroke (IS), showing their effectiveness in separate studies.

Purpose of the study

to study the effectiveness of treatment of ischemic stroke in the acute period with a complex of neuroprotective drugs.

Materials and Methods

We for the period 2018–2020. 154 patients with IS in the acute period were examined at the age of 41 - 81 years (average age 60.56 ± 0.60 years), of which there were 101 men, 53 women. The average age of the observed men was 60.63 ± 0.77 years, women - 60.42 ± 0.94 years.

Results

By simple randomization, the patients were divided into two groups with different treatment regimens. The main characteristics of the patients who took part in the study are presented in Table 1.

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Table 1. Frequency and Severity of Cognitive Impairment

Index	Main group	Control group
Number of patients, n (%)	85 (55,19%)	69 (44,81%)
Average age, years, (M ± δ)	60,15±0,92	60,17±0,88
Men, n (%)	56 (65,88%)	45 (65,22%)
Women, n (%)	29 (34,12%)	24 (34,78%)
Pathogenetic variant of stroke (according to TOAST criteria), n (%)		
Atherothrombotic	42 (49,41%)	37 (53,62%)
Cardoembolic	34 (40%)	24 (34,78%)
Lacunar	9 (10,59%)	6 (8,70%)
Hemodynamic	0	2 (2,90%)
AI localization:		
Carotid basin, n (%)	68 (80%)	52 (75,36%)
ВББ, n (%)	17 (20%)	17 (24,64%)
Hospital admission from the moment of stroke, n (%):		
up to 3 hours	22(25,88%)	17(24,64%)
3-6 hours	14 (16,47%)	18(26,09%)
6-12 hours	20(23,53%)	18(26,09%)
12-24 hours	14(16,47%)	6(8,70%)
24-36hrs	15(17,65%)	10(14,49%)
Risk factors n (%)		
AG	82(96,47%)	63 (91,30%)
Arrhythmias	43 (50,59%)	28(40,58%)
Ischemic heart disease	48(56,47%)	33 (47,83%)
Diabetes	14(16,47%)	7 (10,14%)
Indicators of indices and scales		
Body mass index, Me [25%; 75%]	28,2 [24,9; 31,1]	26,7 [24; 30,8]
Average score of Orgogoz on admission, Me [25%; 75%]	50 [35; 75]	45 [30; 65]
Average NIHSS score at admission, Me [25%; 75%]	10 [8; 14]	10 [7; 14]
Lethal outcome, n (%)	2(2,35%)	6(8,70%)

Patients in both groups were matched for gender and age. In most cases, there was an atherothrombotic subtype of stroke, which coincides with the literature data on its predominance among the pathogenetic variants of cerebral infarction [5].

The effectiveness of combined neuroprotective therapy was studied in three subgroups of patients - with IS in CB of moderate severity (7-14 points on the NIHSS scale) (National Institutes of Health Stroke Scale, National Institutes of Health Stroke Scale), severe IS in KB (15 or more points on the scale NIHSS), and AI into the vertebrobasilar basin. These groups were designated as the main ones. The results of the studies in each main group were compared with the control groups, similar in clinical terms and receiving standard treatment.

Complete dependence on others in the main group was observed in 2 patients (4.34%), in the CG - in 6 (16.22%). By the time of discharge from the hospital, in the group receiving combined neuroprotective therapy, patients with mild and moderate dependence prevailed, in the group receiving standard therapy - with severe and complete ones.

On the first day of observation in the main group there was an increased level of CRP, which decreased by the 5th day ($p < 0.001$ compared with the CG). In the CG, despite the lower initial level, CRP tended to increase during the observation period. Such dynamics may indicate a positive effect of neuroprotective therapy not only on metabolic, but also on inflammatory processes in IS.

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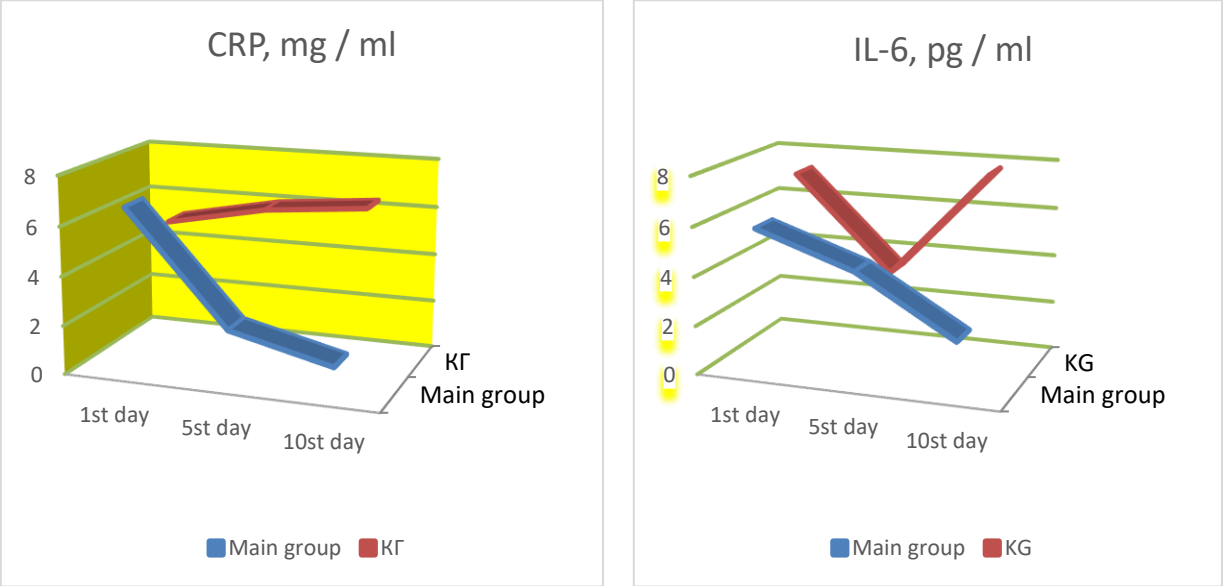
Changes in the proinflammatory cytokine IL-6 during treatment in the study group were similar to the direction of the CRP dynamics - during the first 10 days, a decrease in the level of IL-6 was observed, while in the control, by the 10th day, there was an increase in the indicator (p <0, 05 versus KG). The level of IL-6 on admission was higher in the age group over 65 - 10.8 [8; 12.7] pg / ml, while in patients <65 years of age 6.15 [4.35; 7.1] pg / ml, p = 0.005.



Rice 2. Dynamics of CRP and IL-6 in the main and control groups of IS into the carotid basin of moderate severity

The above observation illustrates a combination of high risk factors for vascular brain damage (age, arrhythmia, arterial hypertension, anemia) in a patient that preceded stroke and severe speech disorders as a manifestation of stroke. Such a status of the patient did not give grounds for a rapid recovery of neurological functions. Nevertheless, it was the combined neuroprotective therapy, in our opinion, that caused the active regression of neurological deficit already in the acute phase of stroke.

Conclusion

In the study of the effectiveness of neuroprotective therapy, positive dynamics by the end of the acute period of IS in the carotid pool of moderate severity according to the NIHSS and Orgogozo scales was 4 [2.5; 5] and 15 [10; 27] points in the main group, respectively, in the control group - 2 [1; 4] and 10 [0; 20]. At the same time, the difference between the main and control groups was statistically significant. Differences were noted in the general course of the pathological process in the studied groups: 3 patients died in the CG, neurological deficit increased in 2 patients, and in two more, focal symptoms remained unchanged.

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