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RESTORATION OF BIOMARKER LEVELS IN ISCHEMIC STROKE

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Abstract
To quickly assess the condition and develop an individual treatment plan in patients with ischemic stroke and low levels of PLA2G2E, DGLA, and PADI4 biomarkers, it is recommended to use the Rankine, Rivermead, MoCA and NIHSS scales. Studies have also established the effectiveness of correcting standard therapy for ischemic stroke by including the nootropic oxiracetam, the dietary supplement GLA, the restoring deficiency of DGLA and the anticoagulant rivaroxaban, which significantly reduce the duration and adverse outcomes of rehabilitation compared with conventional therapy.

Keywords: Ischemic stroke, PLA2G2E, DGLA and PADI4, D-dimer, miR-210.

Introduction

Stroke, due to the peculiarities of its development, occupies a special place among other diseases. An analysis of 29 studies revealed that its prevalence exceeds 2%, while in most studies the indicator varies from 1% to 3%. These data reflect the overall prevalence of stroke in the studied populations [1].

Treatment of ischemic stroke (IS) is carried out in accordance with modern Russian and international standards. Therapy includes a set of measures aimed at:

- Correction of the water-electrolyte balance.
- Maintaining adequate blood oxygenation.
- Blood glucose monitoring.
- Prevention of hyperthermia and seizures.
- Reduction of intracranial pressure.

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In addition, neuroprotective and antioxidant therapy, the appointment of anticoagulants and antiplatelet agents, as well as ensuring adequate nutritional status are recommended.

A new generation anticoagulant, rivaroxaban, is of particular interest. This drug is a highly selective direct inhibitor of factor Xa, is characterized by high oral bioavailability and demonstrates efficacy comparable to warfarin in the prevention of thromboembolic complications in patients with non-valvular atrial fibrillation. Experience has been gained in the use of new oral anticoagulants (NOACs) as an alternative to vitamin K antagonists (AVCS) for long-term prevention of stroke and other conditions associated with an increased risk of thrombosis [2-5].

In the context of the prevention and treatment of stroke, especially ischemic stroke, it is important to take into account not only the acute phase, but also the long-term perspective. The use of rivaroxaban as an alternative to warfarin or AVK opens up new possibilities for patients in need of long-term anticoagulant therapy. The convenience of oral administration and predictable pharmacokinetics of the drug can help increase patient adherence to treatment and, as a result, reduce the risk of recurrent strokes and other thromboembolic complications.

However, when prescribing anticoagulant therapy, it is necessary to take into account the individual characteristics of each patient, including the presence of concomitant diseases, an assessment of the risk of bleeding and potential drug interactions. Careful monitoring of the patient's condition and regular evaluation of the effectiveness and safety of therapy are key to achieving optimal results.

To optimize stroke prevention and treatment strategies, further research is needed to investigate the long-term efficacy and safety of rivaroxaban and other NOACs in various groups of patients at risk of stroke. It is also important to investigate the effects of these drugs on cognitive function and quality of life in stroke patients.

The study is aimed at determining the effectiveness of rivaroxaban in the rehabilitation program for patients with acute ischemic stroke. The effectiveness

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is assessed using neuroimaging and biochemical methods, which will determine the feasibility of including rivaroxaban in the rehabilitation process.

Materials

The object of this study were two clinical cohorts of patients (n = 176) hospitalized with a diagnosis of acute ischemic stroke.

To ensure uniformity of the sample, patients with the atherothrombotic subtype of stroke were selected as the most common. The patients were divided into three groups:

Group A (n=98): Patients with elevated concentrations of signaling biomarkers: digomo-γ-linolenic acid (DGLA), phospholipase A2 group IIE (PLA2G2E) and peptidylarginine deiminase 4 (PADI4), who received only basic therapy.

Group B (n=40): Patients with low levels of these markers who received anticoagulant (rivaroxaban 20 mg) and oxiracetam along with basic therapy. In addition, to increase the level of DGLA, as the first link of the triad, patients in this group were prescribed a dietary supplement – Borage oil [6].

Group C (n=38): Patients with low levels of these markers who, like group A, received only basic therapy.

The average age of the patients in the groups was 62.8 ± 0.91 years. Among them, 67.1% were men (average age 61.4 ± 1.42 years) and 32.9% were women (average age 61.1 ± 1.55 years). Upon admission, all patients underwent a standard clinical and neurological examination. The degree and nature of cognitive impairments, the dynamics of their development were assessed, as well as a detailed analysis of somatic and neurological statuses. The diagnosis was carried out in accordance with ICD-10.

Treatment regimen: Group B on the background of standard therapy, patients received rivaroxaban in tablets of 20 mg once a day. To increase DGLA levels, borage oil was prescribed to patients at a dose of 150 mg (10 drops) three times a day with oral meals for 3 months. The choice of dose was based on data from previous studies that showed the effectiveness of borage oil in increasing serum DGLA levels in dermatitis [6]. The dose was adjusted to take into account the possible partial decomposition of the oil in the stomach.

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Oxiracetam was prescribed according to the following regimen: intravenously as an injectable solution at a dose of 4-6 g per day for 21 days, followed by oral administration of 2 capsules 2-3 times a day. The total duration of therapy in groups (A, B, and C) was 3 months.

The severity of craniocerebral innervation insufficiency, motor sphere, muscle tone, tendon reflexes, the presence of pathological signs, coordination and sensitivity disorders, as well as disorders of higher brain functions was assessed by determining the level of a triad of biomarkers (PLA2G2E, DGLA and PADI4) and microRNA-210 (miR-210). These biomarkers are called the triad because of their close correlation in functional indicators.

The effectiveness of rivaroxaban was monitored by monitoring the level of D-dimer in the blood. An increase in the level of D-dimer, according to literature data, may be a risk factor for recurrent stroke and, therefore, its indicators reflect the effectiveness of the anticoagulant therapy used.

Results and Discussion

A biochemical analysis of the content of key markers of the inflammatory-metabolic triad — PLA2G2E (phospholipase A2 of group IIE), DGLA (digomo-gamma-linolenic acid) and PADI4 (peptidylarginine deiminase) - in the blood serum of patients with ischemic stroke (IS) demonstrated significant differences between the groups with different functional status.

Before the start of rehabilitation measures, the PLA2G2E content in patients in groups B and C was 0.592 ± 0.12 units and 0.583 ± 0.11 units, respectively, while in the main A group this indicator was significantly higher — 0.912 ± 0.14 units. At the end of the three-month therapy, an increase in values was observed in the groups: up to 0.788 ± 0.18 units. in patients in the group, 0.612 ± 0.10 units. in patients from group I to 0.998 ± 0.17 units. in patients of group A, this indicates greater metabolic activity and preservation of the inflammatory response in the latter. This may reflect a more active work of neurons, immune cells, and regeneration processes (Fig. 1).

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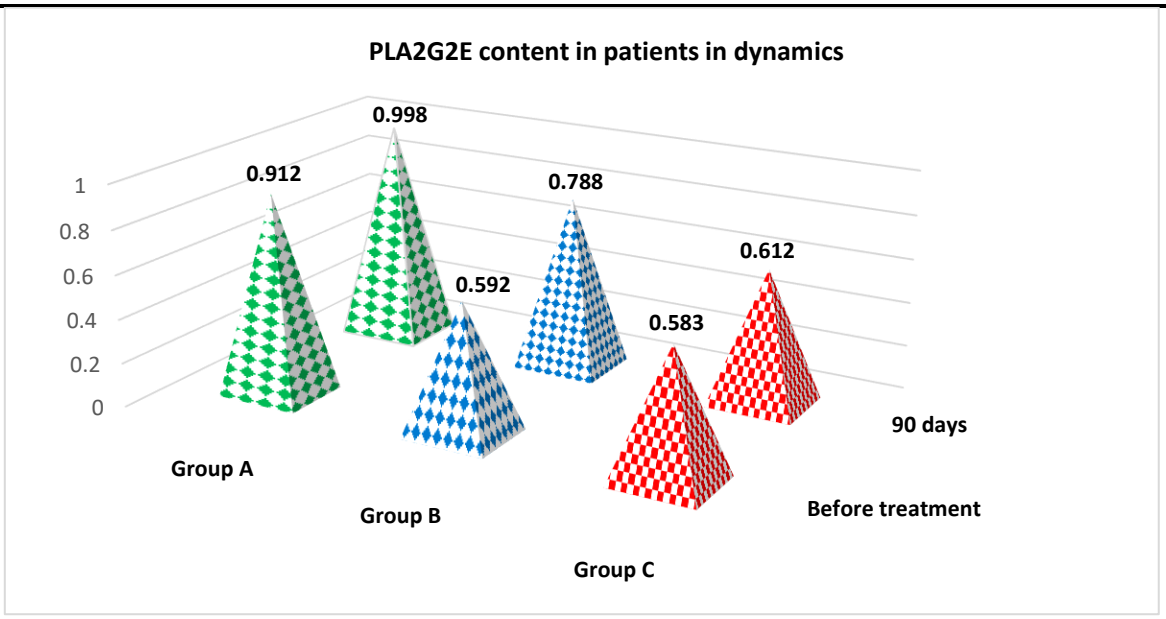

Figure 1.

Similarly, DGLA levels before treatment in group B and C were at 2.39 ± 0.44% and 2.31 ± 0.41%, respectively, whereas in group A it was 3.84 ± 0.61%. After three months of therapy, the DGLA level increased to 3.84 ± 0.52% in group B and to 2.65 ± 0.46% in group C and reached 4.62 ± 0.85% in group A, indicating marked activation of lipid metabolism under conditions of higher initial PLA2G2E expression (Fig. 2).

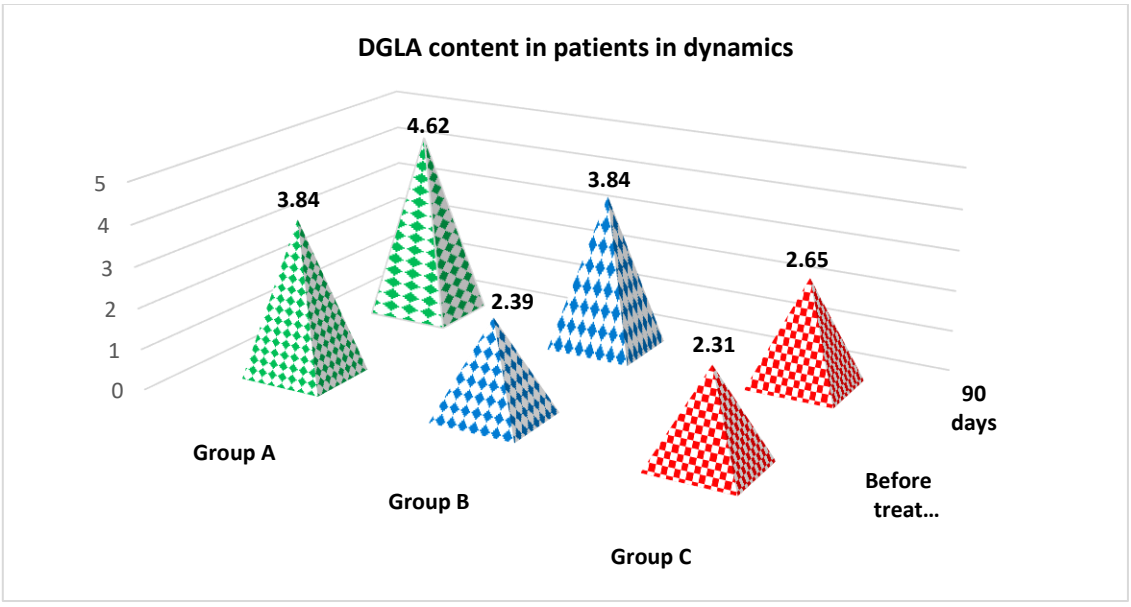

Figure 2.

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The level of PADI4 before treatment in group B and C was 61.4 ± 2.33 u/ml and 60.2 ± 2.21 u/ml, respectively, which is significantly lower than in group A — 223.4 ± 8.62 u/ml. Upon completion of the rehabilitation course, PADI4 values in group B increased to 114.8 ± 5.62 u/ml and in group C to 78.8 ± 3.12 u/ml, and in group A to 298.8 ± 10.8 u/ml, demonstrating significant activation of epigenetic mechanisms responsible for cellular adaptation and inflammatory regulation (Fig.3).

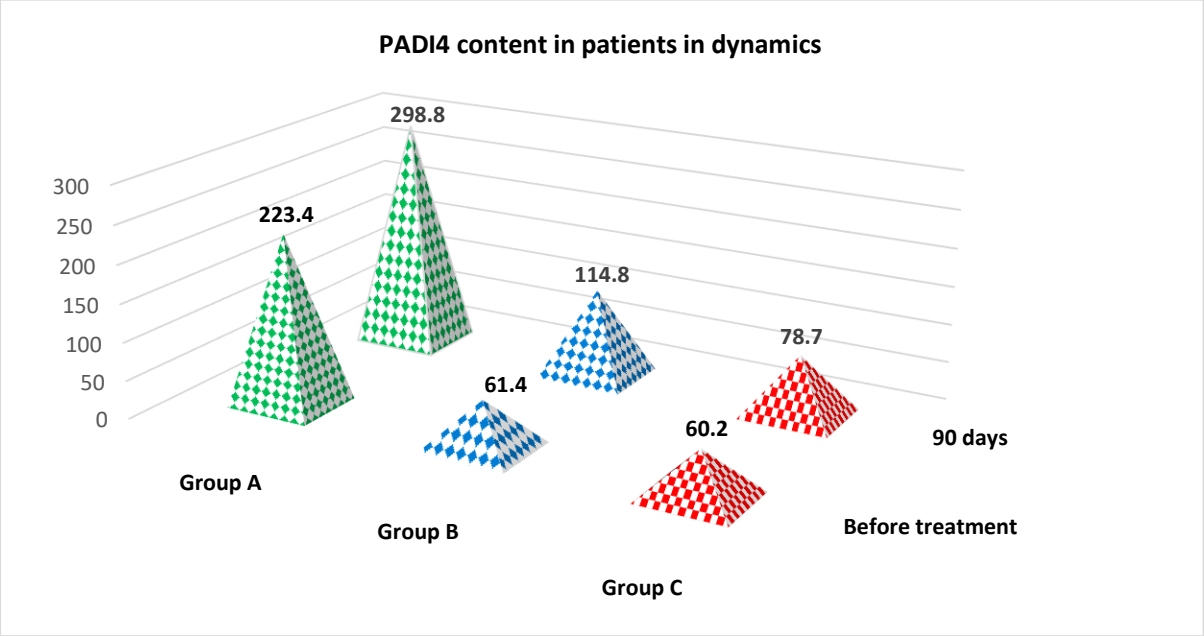

Figure 3.

The data obtained confirm that the regenerative potential and the degree of recovery processes after ischemic stroke depend on the initial activity level of the PLA2G2E–DGLA–PADI4 metabolic triad. A higher level of these biomarkers in the A group of patients contributes to better adaptation of the neural environment, activation of reparative processes, reduction of the systemic inflammatory background and, as a result, improvement of clinical and functional outcomes. This underlines the importance of evaluating this triad as a predictive criterion for the effectiveness of rehabilitation and a possible target of therapy in the post-stroke period.

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If the D-dimer content in groups B and C before treatment was 684.4 – 688.2 ng/ml, then the dynamics decreased significantly after 10 days of treatment and after 3 months, but to varying degrees, and more pronounced in group B, who received combination therapy (Fig.4).

These data confirm not only the normalization of hemostasis, but also the high effectiveness of the therapy in terms of secondary prevention of thrombotic events, including recurrent stroke

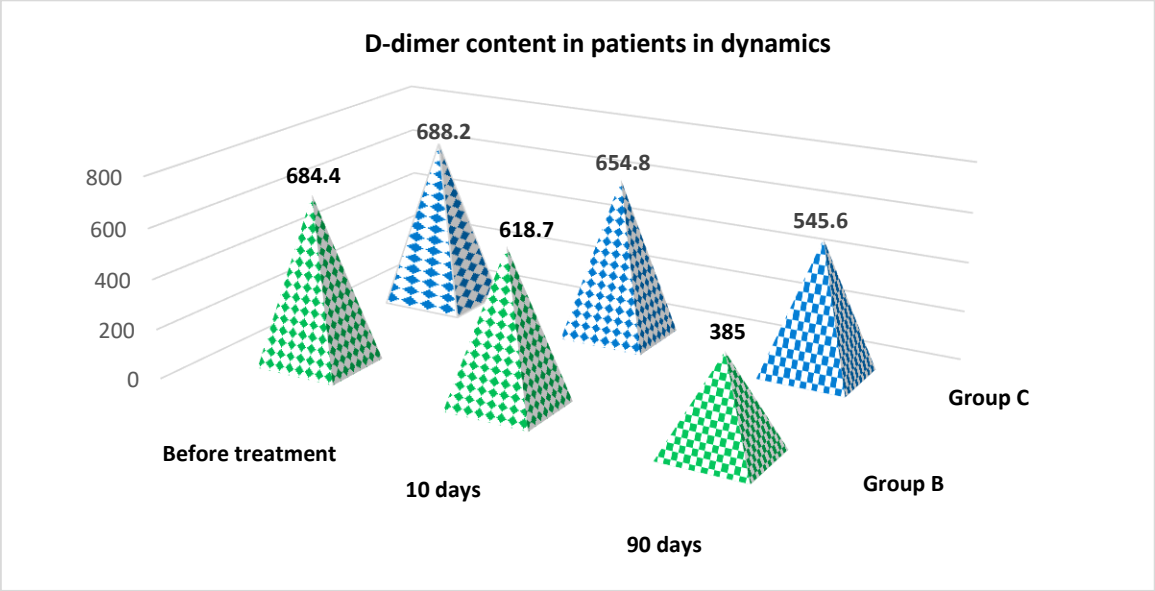

Figure 4.

The analysis clearly demonstrates that in group B, the anticoagulant response was sufficient, and a certain proportion of patients with persistent elevated D-dimer values indicate a normal response of the group to the use of an anticoagulant. These data are consistent with literature evidence that lowering the level of D-dimer is a reliable biomarker for reducing the risk of recurrent stroke, especially in the case of inadequate fibrinolytic control.

Thus, the results obtained confirm that an integrated approach to therapy in group B contributes to the effective restoration of hemostatic balance and reduction of thrombotic risks.

Analysis of the average levels of MIR-210 (miR-210), one of the key regulators of cellular adaptation, neuroinflammation, and angiogenesis, showed marked

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differences between the study groups both before and after the rehabilitation course.

Before treatment, the miR-210 content in group B patients was 2,650,312 ± 11,844 copies, reflecting a decrease in the activity of the molecular mechanisms of regeneration and repair. At the same time, in the main (A) group, the level of miR-21 was significantly higher — 5,254,657 ± 19,544 copies, which may indicate a more pronounced activation of protective and adaptive processes against the background of increased metabolic activity.

After a 90-day course of standard therapy, the level of miR-21 in group B patients increased unprincipledly to 2,967,822 ± 13,756 copies, whereas in group A, stable maintenance of high levels was observed — 5,538,354 ± 19,988 copies, indicating stable expression of this regulator in conditions of a more favorable neurobiological background. In group C patients, there was a slight increase (Fig.5).

The data obtained confirm that patients with a higher baseline level of the triad of biomarkers (PLA2G2E, DGLA, PADI4) demonstrate significantly higher expression of miR-210, both before and after treatment, which may be associated with more active mechanisms of neurotransmission and anti-inflammatory regulation. While in patients with low triad levels, miR-210 activity remained at a limited level even after rehabilitation, which probably limits the potential of neuroplasticity and contributes to delayed recovery.

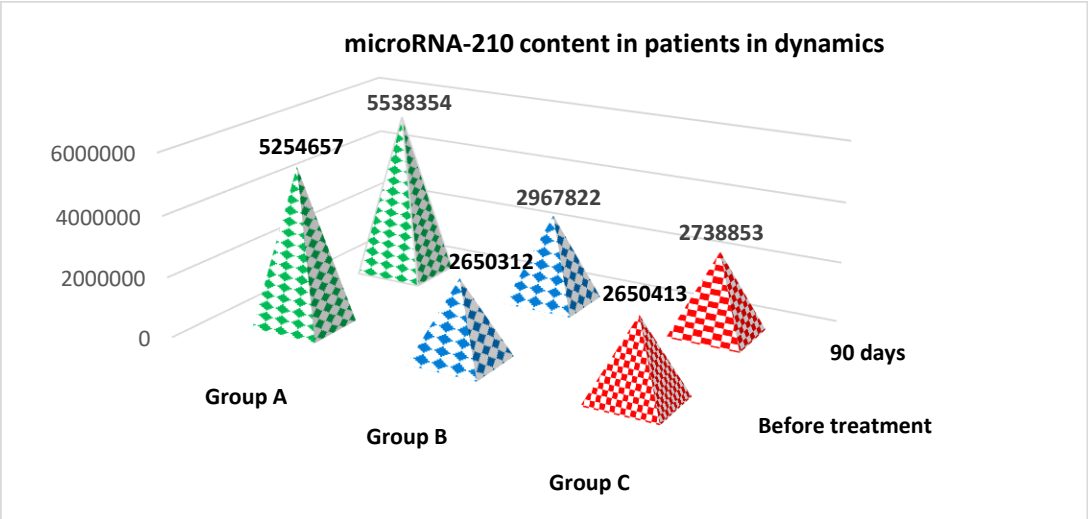

Figure 5.

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The results of the study of the sensitivity and information content of the selected markers showed that the use of rivaroxaban in combination with the nootropic oxiracetam and the dietary supplement GLA helps to accelerate the processes of neuroplasticity and shorten the rehabilitation period.

An analysis of the dynamics of neurological parameters in patients receiving additional therapy in addition to the standard one revealed the positive effect of correction of rehabilitation procedures on the restoration of functional activity of trophic systems of the brain, as well as on trophism and regeneration of cholinergic neurons of the central nervous system.

Conclusion

An integrated approach to the treatment of patients with ischemic stroke (IS) and low levels of the triad of biomarkers (PLA2G2E, DGLA, and PADI4) and microRNA-210 (miR-210), including rivaroxaban, oxiracetam, and GLA in standard therapy, has demonstrated effectiveness in reducing the recovery time of the studied functions.

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