Case Report

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Systemic Thrombolytic Therapy for Ischemic Stroke in the Course of Anticoagulants

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SUMMARY This article reports the first experience of the N.V. Sklifosovsky Research Institute for Emergency Medicine in reperfusion therapy for ischemic stroke in a patient taking oral anticoagulant.

Keywords: acute cerebrovascular accident, atrial fibrillation, dabigatran etexilate , idarucizumab, thrombolytic therapy

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APTT – activated partial thromboplastin time
ASPECTS – Alberta Stroke Program Early CT score
crt-RA – recombinant tissue plasminogen activator
ECASS – European Cooperative Acute Stroke Study

ECG – electrocardiography
HR – heart rate
INR – international normalized ratio
IS – ischemic stroke
MCA – middle cerebral artery
MRI – magnetic resonance imaging
NIHSS – National Institutes of Health Stroke Scale
NINDS – National Institute of Neurological Disorders and Stroke
sTLT – systemic thrombolytic therapy
TT – thrombin time

INTRODUCTION

The incidence of repeated acute cerebrovascular accidents or systemic embolism in patients with atrial fibrillation taking oral anticoagulants is about 1.1–2.2% per year [1–4]. Currently, reperfusion therapy (RT) is the main method of treating patients with ischemic stroke (IS) [5]. The safety and efficacy of systemic thrombolytic therapy (sTLT) with recombinant tissue plasminogen activator *(rt-PA)* in patients with IS within 3 hours, and then 4.5 hours from the onset of symptoms of the disease was demonstrated in the *NINDS* (1995) and *ECASS* III (2008) studies [6, 7].

According to the American guidelines for the diagnosis and treatment of IS, the use of *rt-PA is* contraindicated in patients taking oral anticoagulants [5]. However, sTLT may be considered in these patients if such indicators as the international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), ecarin clotting time, coagulation factor Xa activity are not increased [5].

The above has created the prerequisites for the development of specific antagonists of oral anticoagulants, which can be used in case of need for systemic thrombolysis in patients taking oral anticoagulants. In the *RE-VERSE AD* study , it was shown that the use of idarucizumab in emergency situations led to a rapid and sustained elimination of the dabigatran-induced anticoagulant effect [8–10]. In 2018, idarucizumab was registered on the territory of the Russian Federation, and in 2019 the All-Russian Scientific Society of Neurologists published a clinical protocol for reperfusion therapy of IS, where the possibility of sTLT in patients taking dabigatran etexilate is acceptable after using idarucizumab [11].

The aim of the article is to show the possibility of performing sTLT after using idarucizumab in a patient taking dabigatran etexilate.

MATERIAL AND METHODS

This article describes a clinical observation during systemic thrombolytic therapy after the use of idarucizumab in a patient with a long history of taking dabigatran etexilate.

Case report

An 84-year-old female patient was delivered by an ambulance team to the N.V. Sklifosovsky Research Institute for Emergency Medicine, 2 hours after the onset of the development of acute neurological symptoms. Neurological status: normal consciousness (Glasgow coma scale score 15), dysarthria, motor aphasia, decreased muscle strength in the right extremities to 4 points, as well as dysphagia and asymmetry of the lower mimic muscles on the right. According to the *National Institutes of Health Stroke Scale (NIHSS),* stroke severity was score 10. Objective status: weight 70 kg, blood pressure 150/90 mm Hg, heart rate (HR) 88 beats per minute, arrhythmic pulse. It is known from the anamnesis that the patient suffers from diabetes mellitus, essential hypertension, as well as a permanent form of atrial fibrillation for a long time, and therefore takes dabigatran etexilate, 110 mg 2 times a day. Considering the clinical picture of acute cerebrovascular accident, computed tomography (CT) of the brain was performed, as well as cerebral CT angiography, which revealed occlusion of the distal M1 segment of the left middle cerebral artery (Fig. 1). *Alberta Stroke Program Early CT score (ASPECTS) 10.*

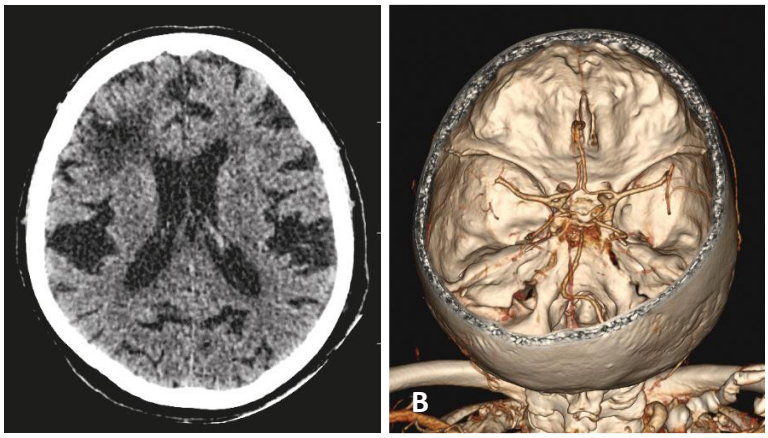

Fig. 1. A - computed tomography of the brain, cystic-atrophic changes in the right frontal lobe; B - CT angiography of intracranial vessels, 3D-reconstruction. The arrow indicates the occlusion of the M1 segment of the left middle cerebral artery

According to the results of electrocardiography (ECG), a tachysystolic form of atrial fibrillation with a heart rate of 117 beats was registered. A biochemical blood test showed a moderate increase in the level of nitrogenous bases (creatinine 103.63 mmol/l , urea 7.88 mmol/l), glycemia 10.9 mmol/l. When examining the hemostasis system, no abnormalities were found: INR 1.12, APTT 35 sec, TT 25 sec, platelets 191 · 10^{9}/l. The creatinine clearance calculated using the Cockcroft-Gault equation was 38 ml/min.

Considering the acute onset of focal neurological symptoms, a history of such risk factors for IS as atrial fibrillation, diabetes mellitus and arterial hypertension, as well as the results of CT of the brain and cerebral CT angiography, IS with thrombosis of the left middle cerebral artery was diagnosed.

Prior to TLT, in order to inactivate the anticoagulant effect of dabigatran etexilate, a specific antagonist of this drug, idarucizumab, was used, which was injected intravenously twice, 2.5 g each for 10 minutes. After that, venous blood was taken to determine the thrombin time and, without waiting for the results, sTLT was started with *rt-PA* at a dose of 0.9 mg/kg of body weight. Taking into account the patient's body weight, the total dose of *rt-PA* was 63 mg, of which 6.3 mg was administered as a bolus over 1 minute, and 56.7 mg over 60 minutes. After 20 minutes, the result of thrombin time was 16.6 s. Considering thrombosis of a large cerebral artery (M1 segment of the middle cerebral artery - MCA), without waiting for the clinical effect of *rt-PA* administration, the patient was admitted to the X-ray operating room in order to perform thrombectomy from the M1 segment of the left MCA. During the transportation of the patient to the X-ray operating room, there was a positive dynamics in the neurological status - an increase in muscle strength in the right limbs, regression of aphasia and dysarthria; the *NIHSS* score was 2.

Digital subtraction angiography revealed restoration of blood flow in the left MCA, and therefore thrombectomy was not performed (Fig. 2). The patient was admitted to the neurological intensive care unit to monitor vital functions.

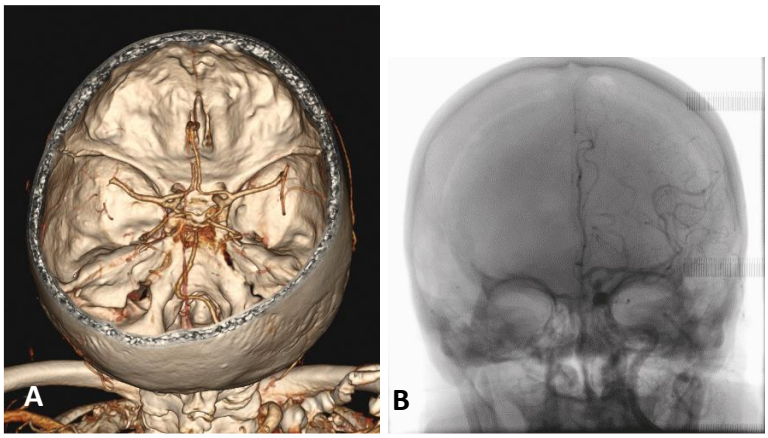

Fig. 2. Digital subtraction angiography. Restoration of blood flow in the left middle cerebral artery

As part of the examination, an ultrasound examination of the brachiocephalic vessels was performed; stenosis of the left internal carotid artery up to 35-40% was revealed. According to transthoracic echocardiography, the ejection fraction was 58%, dilatation of the left atrium up to 47 mm, and mitral valve regurgitation of the 2-3rd degree were revealed. To exclude hemorrhagic transformation, CT scan of the brain was performed 24 hours after the start of sTLT; no signs of intracranial hemorrhage or ischemic changes were found (Fig. 3).

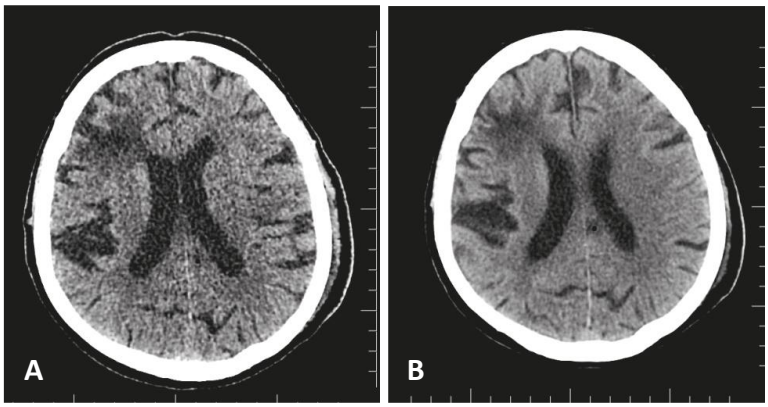

Fig. 3. Computed tomography of the brain 24 hours after the thrombolytic therapy. No foci of acute cerebral ischemia

On the 4th day of hospitalization, the patient underwent magnetic resonance imaging (MRI) of the brain, multiple foci of acute cerebral ischemia in the left MCA circulation were verified without radiological signs of hemorrhagic transformation (Fig. 4).

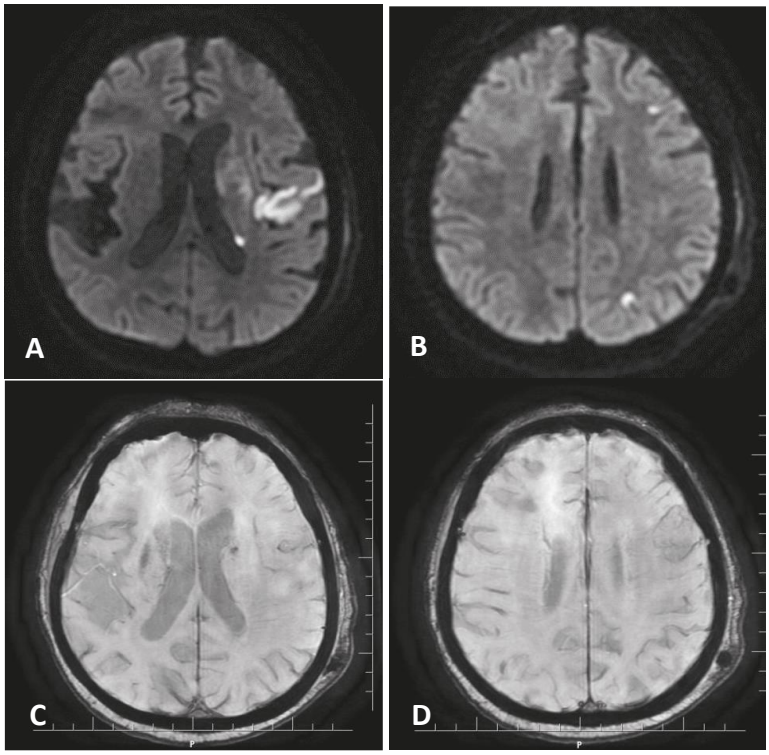

Fig. 4. Magnetic resonance imaging of the brain: A, B - diffusion-weighted image (DWI mode), arrows indicate areas of diffusion limitation corresponding to acute cerebral ischemia; C, D - T2 star weighted angiography, no hemorrhagic transformation revealed

On the 4th day of the disease, the patient underwent transesophageal ECG, loose thrombotic masses were revealed in the left atrial appendage. Warfarin was prescribed for secondary prevention. The target INR value was achieved one week after the start of warfarin administration and amounted to 2.95. In order to assess the effectiveness of the therapy, on the 14th day of hospitalization, the patient underwent a CT scan of the heart with contrast enhancement, where signs of thrombosis in the left atrial appendage persisted (Fig. 5).

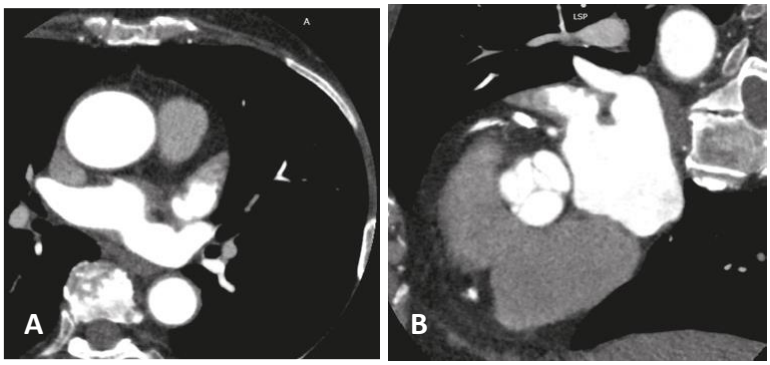

Fig. 5. Computed tomography of the heart: A - axial section, the arrow indicates the contrast defect of the left atrial appendage; B - multiplanar reconstruction along the long axis and the left atrial appendage, the arrow indicates the contrast defect

On the 16th day, the patient was discharged with minimal neurological deficit (*NIHSS* 1, Rivermead activity index 15, Bartel index 100, modified Rankin scale 1) with recommendations on the continuation of anticoagulant therapy and repeated transesophageal ECG in 3 months.

DISCUSSION

The use of oral anticoagulants in patients with IS and nonvalvular atrial fibrillation has shown its high efficiency and safety in preventing recurrent acute cerebrovascular accidents and/or systemic embolism. Nevertheless, in 1.1-2.2% of patients receiving OAC, repeated IS develops. Moreover, this group of patients may experience emergency conditions requiring immediate neutralization of the anticoagulant effect of OAC. Thus, modern OAC should have a specific antagonist capable of reversing the anticoagulant effect caused by it in the shortest possible time.

In the presented clinical case, a patient with nonvalvular atrial fibrillation developed IS while taking dabigatran etexilate, which was a contraindication to sTLT due to the increased risk of symptomatic hemorrhagic transformation. An increase in thrombin time to 25 s indicated the presence of anticoagulation while taking dabigatran etexilate. The anticoagulant effect of dabigatran etexilate was neutralized within 10 minutes by intravenous administration of a specific antagonist, idarucizumab, which was confirmed by the result of a repeated TT blood test.

The TT index after the infusion of idarucizumab decreased to 16.6 s, which corresponded to normal coagulation and made it possible to perform systemic thrombolytic therapy. In the course of sTLT with *rt-PA*, a significant positive dynamics in neurological status was noted - the total *NIHSS* score decreased from the initial 10 to 1. It should also be noted that, despite the occlusion of a large cerebral artery (MCA M1 segment), complete recanalization was achieved without thrombectomy, which was confirmed by digital subtraction angiography. Despite the fact that sTLT was performed in the patient taking OAC, no hemorrhagic transformation was detected during CT scan of the brain in dynamics, as well as MRI.

The current American recommendations for the secondary prevention of IS clearly regulate the prescription of vitamin K antagonists in patients with left atrial thrombosis. In this regard, we performed transesophageal echocardiography, where thrombosis of the left atrial appendage was revealed. For this reason, vitamin K antagonist was prescribed for secondary prevention of IS and systemic embolism in a patient with thrombosis of the left atrial appendage, and transesophageal echocardiography was recommended in 3 months.

CONCLUSION

Despite the prevention of ischemic stroke carried out with the help of oral anticoagulants, ischemic stroke with the need for reperfusion therapy may develop in patients with atrial fibrillation. In patients receiving dabigatran etexilate, TLT may be performed after inactivation of the anticoagulant with idarucizumab. Idarucizumab rapidly reverses the anticoagulant effect of dabigatran.

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