ACUTE ISCHEMIC STROKE IN A PATIENT TAKING DABIGATRAN THAT WAS NEUTRALIZED BY IDARUCIZUMAB BEFORE FIBRINOLYSIS: THE FIRST CLINICALLY SUCCESSFUL CASE IN VIETNAM

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Non-vitamin K antagonist oral anticoagulants are used more and more popularly because they are more effective than vitamin K antagonists. Dabigatran is the only non–vitamin K antagonist oral anticoagulant with an antidote, idarucizumab, in Vietnam. The rate of ischemic stroke while using Dabigatran annually is very rare, only 1.75%. We present the first clinical case in Vietnam using Dabigatran with acute ischemic stroke; patient is a 58 years old female, with history of atrial fibrillation, pacemaker, hypertension, old ischemic stroke, using Dabigatran 150mg, 2 tablets/day. The patient was admitted to the Bach Mai Hospital because of weakness on the right side of the body at the 3rd hour, NIHSS of 10 points, CT scans confirmed acute ischemic stroke due to occlusion of the left M3 segment, the last dose of dabigatran was taken 6 hours prior. The patient was given 2 jars of idarucizumab 2.5g, then rt-PA at a dose of 0.6 mg/kg. The patient improved, the NIHSS score was 3 points, and there was no bleeding in the control CT scan. The patient was discharged after 4 days of treatment, with an mRS score of 1.

Keywords: Ischemic stroke, dabigatran, rtPA, NOAC, idarucimab.

I. INTRODUCTION

Atrial fibrillation is a common cause of cerebral infarction. Anticoagulant is indicated for the prevention of cerebral infarction in patients with atrial fibrillation and thrombosis from the heart.[1,2] New generation oral anticoagulants (NOACs) of two classes of direct thrombin inhibitors (inhibitors of direct thrombin. dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban) has been shown in randomized controlled trials to be superior to vitamin K antagonists concerning the prevention of systemic thrombotic events, cerebral infarction, and bleeding.[3] Although NOACs are superior to warfarin, however, the risk of recurrent ischemic stroke in patients taking NOACs fluctuates by 1 - 2% per year.[3]

According to the American Stroke Association in 2019, it is recommended to use fibrinolytic for patients with acute cerebral infarction within 4.5 hours who are taking vitamin K antagonists with INR < 1.7.[4] At the same time, AHA has not recommended fibrinolysis in patients who are receiving NOACs with a final dose of 48 hours prior the cerebral infarction eventik, unless the extensive coagulation test parameters are precisely known, such as aPTTs, anti-Xa concentration, INR, clot dissolution time, thrombin time.[4]

In Vietnam, there are three NOACs currently prescribed: dabigatran, rivaroxaban, and- apixaban. Dabigatran is the only drug with idarucizumab as antagonist in Vietnam.

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Idarucizumab is indicated for patients receiving dabigatran who require emergency surgery or intervention, or when bleeding is uncontrolled and/or life-threatening.[5]

The French Society of Neurovascular Diseases and the French Society of Hemostasis recommend the use of idarucizumab followed by intravenous thrombolysis in patients receiving NOACs in the last 48 hours.[6] According to the European Stroke Association 2021, patient with acute ischemic stroke within 4,5 hours, who received dabigatran within the previous 48 hours, 8/9 experts agreed to use idarucizumab and rtPA after that rather than not fibrinolysis.[7] However, the extent only stop at expert opinion, currently there is not enough evidence to make any recommendations.[7] As such we use it as the scientific basis for us to apply the regimen of idarucizumab and rtPA for our case.

II. CASE PRESENTATION

A 58-year-old female patient was admitted to Bach Mai Stroke Center because of sudden difficulty with speech and weakness in the left half of her body in the second hour.

The patient had a history of hypertension, atrial fibrillation, permanent pacemaker implantation, heart failure, and three times of cerebral infarction (in 2010, 2014, and 2018) but left with no sequelae. Currently, the patient is on maintenance of Dabigatran 150mg x 2 tablets/day, Uperio 100mg/day, and Spiromide 20/50mg x 1 tablet/day. The patient took the last 150mg dabigatran tablet 5 hours before admission.

Clinical examination on admissionshowed Glasgow 14 points, pupil 2mm, light reflex (+), no blurred vision, no ophthalmoplegia, no nystagmus, difficulty speaking, left central VII paralyzes, hemiplegia left arm strength 2/5, left hemiparesis, NIHSS: 10 points, left arm blood pressure: 120/80mmHg, right arm blood pressure 115/75mmHg, regular heart rate, no murmur, heart rate 70 beats/min, BMI: 24.6, capillary blood sugar 5.7 mmol/l.

Result of MSCT brain angiogram shows old lesion of left fascia, no cerebral bleeding, occlusion of right M3 artery.

After 20 minutes of admission, the patient was rapidly infused with 2 jars of idarucizumab 2.5g over 10 minutes to reverse the effects of dabigatran. After that, the patient received an intravenous infusion of alteplase at a dose of 0.6 mg/kg, a bolus of 15%, and a maintenance dose of 85% of the total dose for 1 hour.

Patient was closely monitored for vital signs and complications such as bleeding, and laryngeal edema in the first 24 hours. The patient only had small bruises at the infusion site, with no clinical bleeding complications. After 24 hours, the patient was completely awake, with left arm muscle strength 5/5, left leg 4/5, no difficulty speaking, no sensory disturbance, NIHSS 1 point.

Result of 32 series cranial computed tomography after 24 hours of fibrinolysis: no bleeding.

Electrocardiogram: Pacemaker rhythm, rate 69 cycles/min.

Laboratory tests were performed on the 2nd day of the illness:

Transthoracic Doppler echocardiography: Left ventricular systolic function reduced EF of 50%, no chamber thrombus, no PFO, moderate mitral regurgitation, multiple tricuspid regurgitations, moderate pulmonary arterial hypertension.

Doppler ultrasound of the carotid artery: no occlusion of the basilar and extracranial vertebral arteries bilaterally.

Doppler ultrasound of lower extremities: no arterial stenosis, no bilateral lower extremity venous thrombosis.

Renal artery Doppler ultrasound: no renal artery occlusion.

After 24 hours of fibrinolysis, the patient had an NIHSS score of 1 and a CT scan of the brain after fibrinolysis: there was little cerebral infarction lesion, and no bleeding transformation. Because the patient had high-risk factors for stroke recurrence as atrial fibrillation without valvular disease, CHA2DS2-VASc score of 5, HAS-BLED score of 2, and history of 3 times cerebral infarction, we decided to use early anticoagulation. Our drug of choice is Pradaxa 150mg, 2 tablets per day. The patient was discharged after 4 days of treatment with an mRS of 1 point.

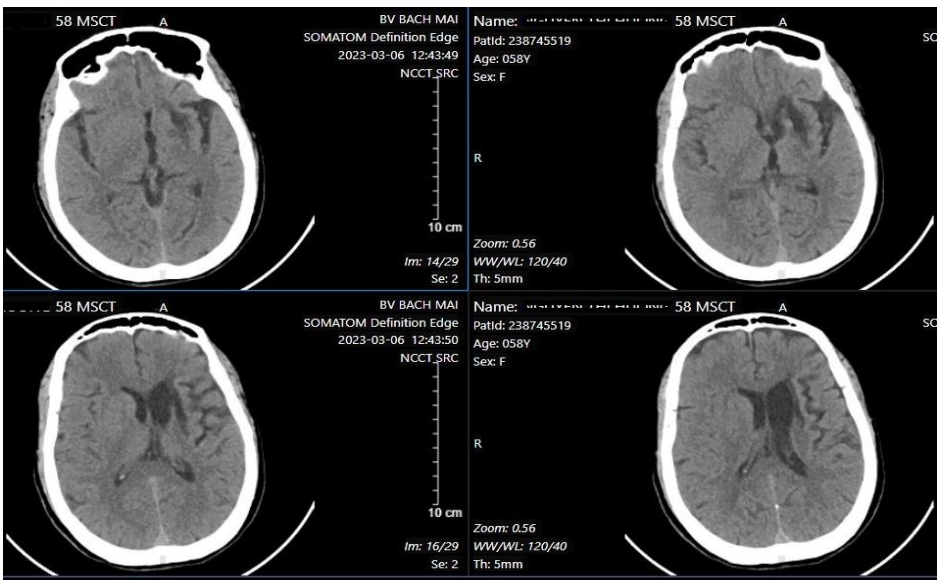

Figure 1. Image of brain parenchyma on CT film at hospital admission

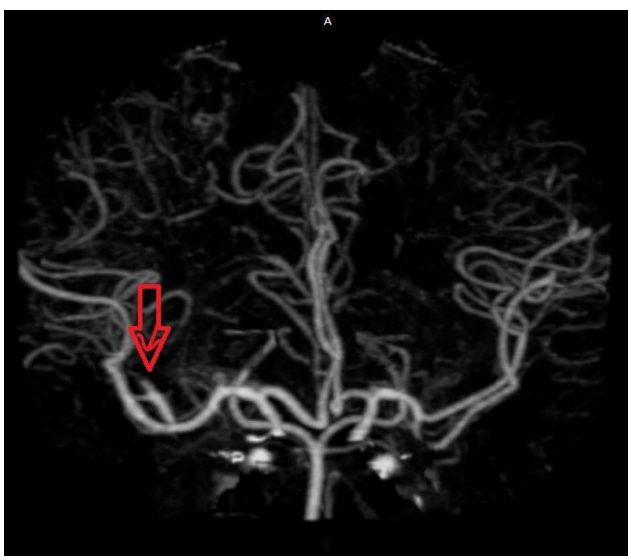

Figure 2. Cerebral vascular image on MSCT film at hospital admission

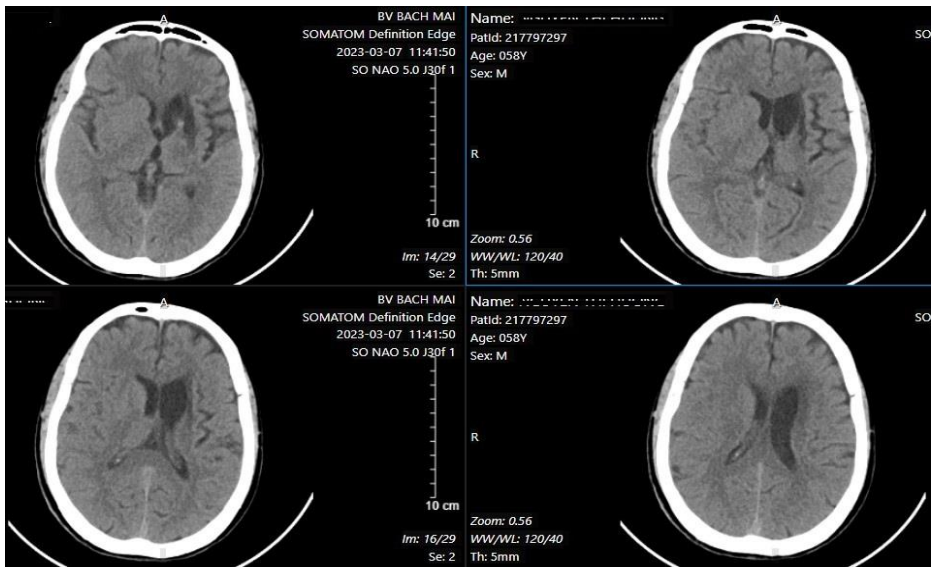

Figure 3. Image of brain parenchyma on CT film 24 hours after fibrinolysis

Table 1. Blood test results

	At hospital admission	After 24 hours
Red blood cells (T/L)	3.97	-
White blood cells (G/L)	9.36	-
Platelets (G/L)	271	-
APTTs/ APTT b/c	23/ 0.78	32.6/ 1.03
PTs/ PT %	14.9/ 82%	11.7/ 94%
INR	1.13	1.06
Fibrinogen (g/dl)	4.96	3.78
D-dimer	-	2.52
Thrombin time (s)	-	15.6
Antithrombin III (%)	-	103
Ure/ Creatinin (mmol/l)	8.3/ 80	-
Na/ K/ Cl (mmol/l)	135/ 4.7/ 99	-
ALT/ AST (U/l)	27/ 21	-
Troponin T hs (ng/L)	24	35
HDL-C/ LDL-C (mmol/l)	-	1.4/ 2.7
Cholesterol/ Triglicerid (mmol/l)	-	4.5/ 0.9
FT4 (pmol/l)/ TSH (uU/ml)	-	16/ 1.74

	At hospital admission	After 24 hours
Vitamin B12 (pmol/l)/ Protein C (%)	-	581/ 114
Anti - dsDNA & ANA (IU/ml)	-	Negative
Anti Phospholipid (U/ml)	-	Negative
Anti B2 - glycoprotein (AU/ml)	-	Negative
Anti Cardiolipin (MPLU/ml)	-	Negative
Lupus anticoagulation (ratio)	-	2.1

IV. DISCUSSION

Idarucizumab, a monoclonal antibody fragment, binds to dabigatran with an affinity 350 times higher than dabigatran and thrombin. Therefore, when idarucizumab binds to free dabigatran and then binds to thrombin, it inactivates dabigatran. In experimental young healthy volunteers with normal renal function, even with mild or moderate renal impairment, the administration of idarucizumab resulted in the immediate and complete reversal of the anticoagulant effects of dabigatran; the FDA has approved the use of idarucizumab in two clinical situations in which patients receiving dabigatran in the past 48 hours that 1) indicate surgery or emergency intervention. or 2) has uncontrolled and/or life-threatening bleeding.[8]

Currently, there is not enough scientific evidence to recommend the routine use of idarucizumab in patients with acute cerebral infarction for 4.5 hours for thrombolysis.[7] A 2020 German retrospective study, which included 120 stroke patients at 61 centers, found that administration of rt-PA after neutralization of dabigatran with idarucizumab for acute ischemic stroke appeared to be effective and safe. 78% of patients improved with a 7 NIHSS reduction from baseline and no bleeding complication.[7] In an observational study in New Zealand, 51 patients were treated with idarucizumab before treatment; thrombosis with the symptomatic intracerebral hemorrhage rate of 3.9% compared with the routine group (without dabigatran) 3.8% was no difference with p = 0.97.[9]

In 2020, author Shima Shahjouei and colleagues performed a meta-analysis that found that the rate of symptomatic conversion bleeding after fibrinolysis in the group of patients with acute ischemic stroke who received DOACs in the previous 48 hours showed no difference in the warfarin group with an INR less than 1.7, with an OR = 0.77 (95%CI: 0.28 - 2.16), and there was no difference compared with the group without prior anticoagulation with OR = 0.92 (95%CI: 0.33 - 2.55).[10]

In 2022, Takashi Okada retrospectively conducted 915 patients with acute cerebral infarction who received fibrinolysis with rtPA at a dose of 0.6 mg/kg, with 40 patients taking DOAC in the 24 hours before stroke onset. Author Takashi found no difference in rates of symptomatic conversion bleeding 36h post fibrinolysis and death in ischemic stroke patients who received DOAC in the 24h before stroke onset compared with no prior anticoagulation. At the same time, the treatment outcome was good, mRS 0-2 in the two groups above was not different.[11]

Further evidence on the benefit and safety of fibrinolysis for patients with cerebral infarction

who took DOACs in the 48 hours before onset is a study by Meinel published in early 2023.[12] The authors showed that a group of patients with acute cerebral infarction who received dabigatran 48 hours before stroke onset, neutralized by idarucizumab, and followed by fibrinolysis did not provide an independent survival benefit. The rate of symptomatic conversion bleeding was lower than that of the control group with unadjusted OR = 0.3 (95%CI: 0.09 - 0.92; p = 0.03).[12]

The above is the basis for us to apply the method of fibrinolysis by Alteplase to our patient with acute cerebral infarction who used dabigatran 6 hours prior. Our patient was admitted to the hospital in the 3rd hour of illness, had a clear time of onset, and was witnessed. On the CT scan of the brain, the damage to the new brain parenchyma is small, there is an old but small infarct lesion. Vascular pulses show occlusion of the right M3 proximal segment, and our facility currently does not have access to this vascular area for mechanical thrombectomy. Therefore, we decided to do fibrinolysis with intravenous Alteplase at a dose of 0,6mg/kg after completing 2 jars of idarucizumab 2.5g. Clinically, the patient improved, the second-day NIHSS score was 3 points. Because the patient has a pacemaker, we performed a CT scan of the brain to assess parenchymal damage after 24 hours of reperfusion therapy. The results showed that there were very few new cerebral infarction lesions, and there was no bleeding transformation.

The strategy of using anticoagulation to prevent recurrent strokes in our patients is very important. Therefore, we planned to re-evaluate and re-learn the patient's pathophysiology. According to the author Polymeris, when a patient is using NOAC drugs and has recurrent cerebral infarction, we need to evaluate: 1) the patient's adherence to the drug; 2) identify the underlying stroke-inducing mechanism; 3) ultrasonography identifies atrial or left atrial thrombus and plans for atrial septal occlusion if possible.[13] The patient undergoes clinical examination to identify other stroke mechanisms that may be associated with atrial fibrillation: carotid Doppler ultrasound did not show stenosis, tests for hypercoagulability, systemic disease were negative, brain angiography did not show intracranial stenosis, echocardiography did not show cardiac chamber thrombosis. Patients adhere to dabigatran anticoagulant very well. Based on the patient's laboratory results, we confirm that the pathogenesis of cerebral infarction is still the cardiac etiology. The reasons we chose dabigatran to continue as the stroke prophylaxis for our patients are: 1) there is currently insufficient evidence to recommend replacement of anticoagulation or the choice of another anticoagulant for this patient. Atrial fibrillation patients on anticoagulation have a recurrent cerebral infarction; 2) in the Vietnam market, only dabigatran has an antidote, while other DOACs do not. If we have patients with recurrent ischemic events, we will continue to use idarucizumab for neutralization and fibrinolysis afterward; therefore, we decided to continue using dabigatran 150mg twice daily from day 2 of the disease to prevent stroke recurrence. The patient was discharged after 4 days of treatment with an mRS score of 1.

V. CONCLUSION

Intravenous fibrinolysis for patients with acute ischemic stroke who received dabigatran within the previous 48 hours from the onset of which was neutered with idarucizumab was safe and resulted in good clinical outcomes. However, we still need evidence from prospective randomized controlled studies to support this finding for future recommendations.

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