

Intravenous Thrombolysis after Reversal of Dabigatran with Idarucizumab in Acute Ischemic Stroke: A Case Report

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Case report

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Abstract

Background: As there is a growing concern about the cerebral embolism events secondary to non-valvular atrial fibrillation, direct oral anticoagulant (DOAC) has been more and more widely used as an anticoagulation treatment for prevention of stroke. However, in the face of life-threatening bleeding or emergency surgery/treatment, doac-related antagonists such as idarucizumab need to be urgently used to reverse the DOAC. Using rt-PA intravenous thrombolysis for acute ischemic stroke requires a time window of 4.5 hours. This case reports rt-PA intravenous thrombolysis after reversal of dabigatran anticoagulation with idarucizumab in patients with acute ischemic stroke.

Case presentation: We report the case of 62-year-old Chinese female with nonvalvular atrial fibrillation treated with dabigatran 110mg twice daily, and missed a dose on the eve of the stroke. The patient presented with acute ischemic stroke causing the angle of mouth deviated to right side and left limb weakness in the early morning of the next day. Due to the last dosing time of dabigatran was between 24-48 hours, the patients were given rt-PA intravenous thrombolysis after reversal of dabigatran anticoagulation with idarucizumab, while all contraindications had been excluded by laboratory test and CT scan. NIHSS score was reduced from 4 to 1, and the patient was discharged after 2 weeks.

Conclusion: Our case report adds to the evidence that idarucizumab administration is safe and effective in the setting of patients with atrial fibrillation treated with dabigatran who develop acute ischemic stroke requiring rt-PA intravenous thrombolysis.

Background:

Acute ischemic stroke is a serious threat to the health of Chinese residents and increased yearly. It is the leading cause of death for urban residents in China and characterised by high morbidity and lethality, high rate of recurrence and disability, and high treatment cost. Cardiac embolism secondary to non-valvular atrial fibrillation (NVAf) accounts for 13-26% of ischemic stroke patients for whom long-term and stable anticoagulant therapy is very important^[1,2]. Compared with warfarin, DOACs significantly reduced the incidence of stroke by 19%, among which dabigatran significantly reduced the incidence of stroke by 34%. There was no significant difference in the overall incidence of major bleeding between the two^[3]. Thus, clinical application of DOACs have been both recommended by "2019 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation" and the "Guideline of stroke prevention in Chinese patients with atrial fibrillation (2017)"^[4,5]. In order to save the patients' lives and improve the prognosis, it is particularly critical to treat the patients with corresponding antagonists when life-threatening bleeding or emergency surgery/treatment occurs in the users of DOAC as their widespread clinical application in China. Idarucizumab is an antagonist of dabigatran and approved in China on February 2019, however, still very limited data on the efficacy and safety data on

idarucizumab use in China. Here we report the first case of acute stroke using rt-PA intravenous thrombolysis after reversal of dabigatran anticoagulation with idarucizumab within the time window of thrombolysis in China.

Case Review:

The 62-year-old female patient was admitted to neurology emergency at 8:50 am on November 1st, 2019, due to "sudden verbal slant accompanied by left limb weakness for 1.5 hours". She was suddenly appeared the left side of the mouth aslant, conscious of numbness and weakness of the limb on the same side, when she was having breakfast in the morning (7:20 am), and could still walk by herself without headache, dizziness, unclear vision, speech deficit or any other manifestations. Her family drove her to the hospital immediately. She had a history of hypertension for more than 30 years without regularly monitoring. The highest blood pressure was 150/100 mmHg, taking valsartan 80mg Qd. She also had a hyperlipidemia history for 6 years, with long-term administration of rosuvastatin 5mg Qn. She was hospitalized in our department of cardiology 6 months ago due to "atrial flutter" and received betaloc 12.5mg twice daily. One month ago she was hospitalized again in another hospital and diagnosed as "pathological sinus syndrome and paroxysmal atrial fibrillation" due to "atrial fibrillation", and was treated with dabigatran 110mg twice daily but without a good compliance. She had no special family history, or history of migraine. Physical examination: BP: 131/81 mmHg (right) 130/84 mmHg (left). There was no uplift or depression in the anterior cardiac area, and the strongest apex pulsation point was 0.5-1.0 cm within the midline of the 5th intercostal left clavicle. There was no lifting pulsation, no tremor or pericardial friction. The relative voiced boundary of the heart is normal. Heart rate: 76 beats/min, regular rhythm, normal cardiac sounds, A2 > P2, no extra cardiac sounds, no cardiac murmurs, no pericardial friction sounds in the auscultation area of each valve.

The patient had clear mind and fluent speech, equal circle of bilateral pupils, direct/indirect response to light exists, and the eyeball moves fully in each direction, without diplopia and nystagmus. The left frontal line, nasolabial groove shallow, show the mouth angle to the right, extending tongue in the center. Double soft palate lift normal, uvula in the middle, pharyngeal reflex normal. Muscle strength of left limb grade V-, bilateral finger nose test and heel-knee-tibia test accurate, bilateral Babinski's sign negative. Hypoesthesia of left limb, Meningeal stimulation negative. Water swallow test normal. Bilateral carotid artery vascular murmur were not heard. NIHSS score: 4 (2 for facial paralysis, left weakness 1, left Numbness 1).

The patient mentioned that she did not take any drugs in the morning and that she missed one dose of dabigatran last night. The last time for taking dabigatran was around 8am the day before. Accordingly, the last DOAC dose taking was between 24-48 hours. Then she had been brought into the emergency fast track for stroke, completed head CT, ECG, blood routine, biochemical and coagulation function test. Her head CT was normal, blood glucose was 5.5 mmol/L, and the ECG showed sinus rhythm of 72 beats/min. Coagulation function results showed APTT 32.7s, PT 12.3s, INR 1.06, CCr 68.62 ml/min. AS ECT and direct prothrombin activity could not be tested, idarucizumab was given at 11:02 am with a dose of 2.5 g,

followed by another 2.5 g at an interval of 5 minutes, and coagulation function was tested again after the administration (Table 1). The rt-PA thrombolysis therapy was initiated at 11:35 am after the completion of the administration of idarucizumab, with a dose of 0.9 mg/kg. During the thrombolysis process, vital signs such as heart rate and blood pressure were monitored, and the NIHSS score was evaluated every 15 minutes (Figure 1). The symptoms of facial paralysis and limb numbness and weakness of the patient were significantly improved after thrombolysis. The NIHSS score was 1 (facial paralysis 1), and the patient was admitted to the stroke ward for further treatment.

Vital signs were monitored within 24 hours after admission, the patient got external auditory canal bleeding 3 hours after thrombolysis. Further more medical history was inquired, and the patient had a history of ear trauma one week ago. Bleeding was stopped by external auditory canal tamponade. The cranial MRI and systemic vascular examination were arranged to find the cause of stroke, no abnormal signal was found in T1, T2 and DWI, and no microhemorrhage was found in SWI (Figure 2). MRA showed intracranial vessels were normal, and bilateral embryonic posterior cerebral arteries were found. Carotid ultrasound showed bilateral carotid intima thickening with plaque formation and plaque was found in right subclavian artery. Arteriovenous ultrasound of lower extremity showed normal. Transcranial Doppler (TCD) showed a rapid increase in the flow rate of the left middle cerebral artery, and 5-6 microembolic could be found in foaming experiment which indicated there may be direct pathway from pulmonary circulation to systemic circulation (RLS). Cardiac systemic examination was completed: 24-hour Holter showed sinus bradycardia, short atrial tachycardia, and atrial premature beats (some of which were not transmitted). Widening ascending aorta was showed on echocardiography. No thrombus was found in Bilateral atrium and left auricle through Transesophageal echocardiography, also no septal shunt beam was observed in the atrial septal fossa ovale. A further review of the data in other hospital before showed left atrium was slightly larger and the middle branch of the right pulmonary vein was mutated on the CTA of the left atria and pulmonary veins at 26th September (Figure 3). Diagnosis of transient ischemic attack (TIA), cardiogenic cerebral embolism, paroxysmal atrial fibrillation, pulmonary arteriovenous fistula, hypertension (Grade 2), and hyperlipidemia were made after admission. She was suggested to restart the anticoagulant treatment deal to the CHA₂DS₂-VAS score was 4 and HAS-BLED score was 2. The pulmonary artery DSA was also be suggested after discharged.

Discussion:

In China, the anticoagulation compliance rate (INR 2.0 ~ 3.0) among the atrial fibrillation patients who are taking the warfarin was only 36% and most of their INR were remained at < 2.0^[6]. In recent years, the anticoagulant treatment has been effectively simplified with the marketing of direct oral anticoagulants. DOAC has been selected by more and more patients with atrial fibrillation in clinical since its efficacy and safety have been confirmed in multiple international clinical trials such as RE-LY^[7]. In our case, embolism stroke still occurred while the patient was taking dabigatran 110 mg twice daily, the two causes maybe considered: the dose of dabigatran was insufficient, it should be adjusted to 150 mg twice daily after stroke. Although the patient was prescribed with dabigatran, she failed to follow medical advice and

took the medicine regularly, which may be an incentive cause for embolism stroke. Therefore, the dosage of dabigatran should be adjusted according to the happening of the embolization stroke and the compliance of patients should be considered in the selection of anticoagulation. In the process of DOAC, doctors and patients are also concerned about the possible life-threatening bleeding such as acute intracranial hemorrhage and massive gastrointestinal bleeding, or the emergency cases such as acute abdominal disease and fracture requiring emergency surgery/treatment. As a specific antagonist of dabigatran, idarucizumab, which has just been approved in China on February 2019, can bind to dabigatran irreversibly and effectively as it has an affinity for dabigatran 350 times than dabigatran for thrombin [8]. In our case, intravenous infusion of idarucizumab lasted for 16 minutes, and rt-PA treatment could be initiated immediately 10-15 minutes later. Idarucizumab could effect immediately that is more suitable for stroke patients within 4.5 hours for intravenous thrombolysis or within 6 hours for arterial thrombectomy in emergency. However, this case also has the following limitations: (1) the patient failed to initiate thrombolytic therapy within 3 hours after the onset because it took a certain amount of time to obtain idarucizumab as we didn't prepare any in emergency. (2) The time of last dose of dabigatran was between 24-48 hrs. Although coagulation indexes, such as APTT and PT and INR index, had been monitored before and after use, no obvious changes were found. The more important coagulation indexes like ECT, TT, and direct prothrombin activity were unavailable in emergency laboratory, so we couldn't judge whether rt-PA could be used without idarucizumab's reversal. It is expected to be improved in similar cases. In a French retrospective research, patients with acute ischemic stroke who were treated with dabigatran within 48 hours were recommended for intravenous thrombolysis after idarucizumab's reversal without direct prothrombin activity monitoring [9]. Giannandrea [10] reviewed 55 thrombolytic cases after idarucizumab reversal of dabigatran showed that 81.9% (45 cases) of patients had improved NIHSS score (median 5 points). In a retrospective study of 120 patients with acute ischemic/hemorrhagic stroke in Germany, the efficacy and safety of idarucizumab reversal of dabigatran in intravenous thrombolysis with acute ischemic stroke had been confirmed. However, in patients with hemorrhagic stroke, the application of can prevent the expansion of hematoma and improve the prognosis of patients [11].

Conclusion:

As the first case of ischemic stroke treated with intravenous thrombolysis after idarucizumab reversal of dabigatran in China, this case belongs to mild stroke (NIHSS \leq 5 points). After treatment, the patient's NIHSS score was significantly improved with a good prognosis. In this case, the efficacy of idarucizumab in the treatment of acute ischemic stroke patients using dabigatran was confirmed, and no directly related side-effects were found, suggesting that idarucizumab could be used as an emergency medication for patients with acute stroke. As the only approved DOAC antagonist in China, the efficacy and safety of idarucizumab need to be confirmed in more clinical cases. Especially in the clinical application of acute stroke patients, the stratification screening in emergency situations, selection of medication and laboratory tests still need to be improved.

Declarations

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Consent for publication

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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- Availability of data and materials ☐ All data and materials of this case can be obtained from the case database of Beijing Friendship Hospital and the image database of Tiantan Hospital
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Tables

Table 1. Hemostasis testing before(1) ,in course of (2) and after (3,4) idarucizumab administration.

	Blood sample1 9:20am 1/11	Blood sample2 11:09am 1/11	Blood sample3 11:18am 1/11	Blood sample4 11:20am 2/11	Reference value of units
Activated Partial Thromboplastin Time(APTT)	32.7	29.4	30.2	31.90	28.00-42.50sec
Prothrombin time(PT)	12.3	12.2	11.7	12.0	11.00-15.00s
Normalized Ratio(INR)	1.06	1.05	1.01	1.04	0.80-1.20
Fibrinogen degradation product(FDP)	0.60	0.80	2.90	1.60	0.00-5.00ug/ml
D-dimers	0.40	0.33	0.70	0.40	0.000- 1.000ug/ml
Fibrinogen(Fbg)	2.64	2.50	2.20	2.08	2.00-4.00g/L
Prothrombin activity(PT(A))	88.1	89.2	94.2	91.4	70.00-120.00%
Antithrombin III	98.9	76.1	90.8	78.8	70.00-120.00%

Figures

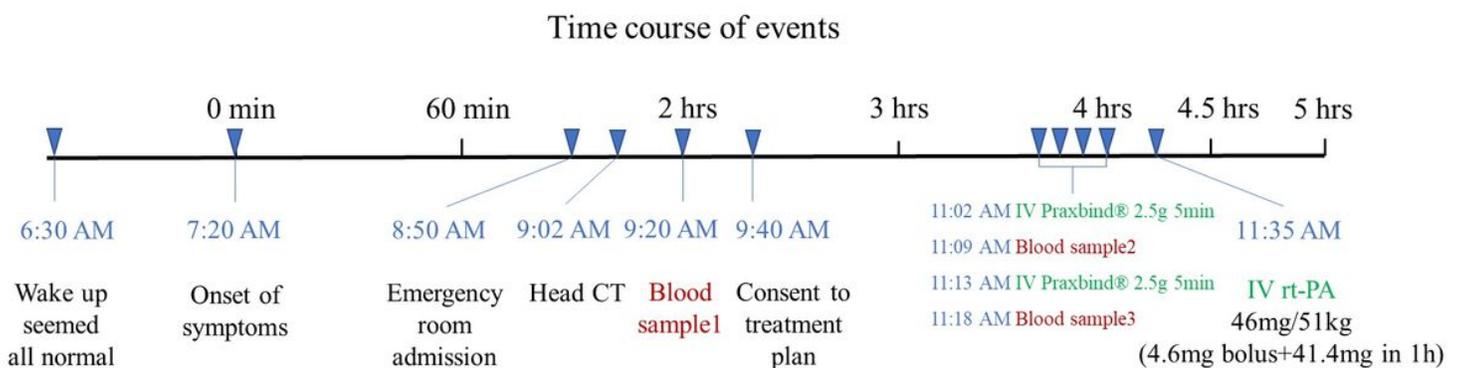


Figure 1. Time course of events

Figure 1

Figure 1

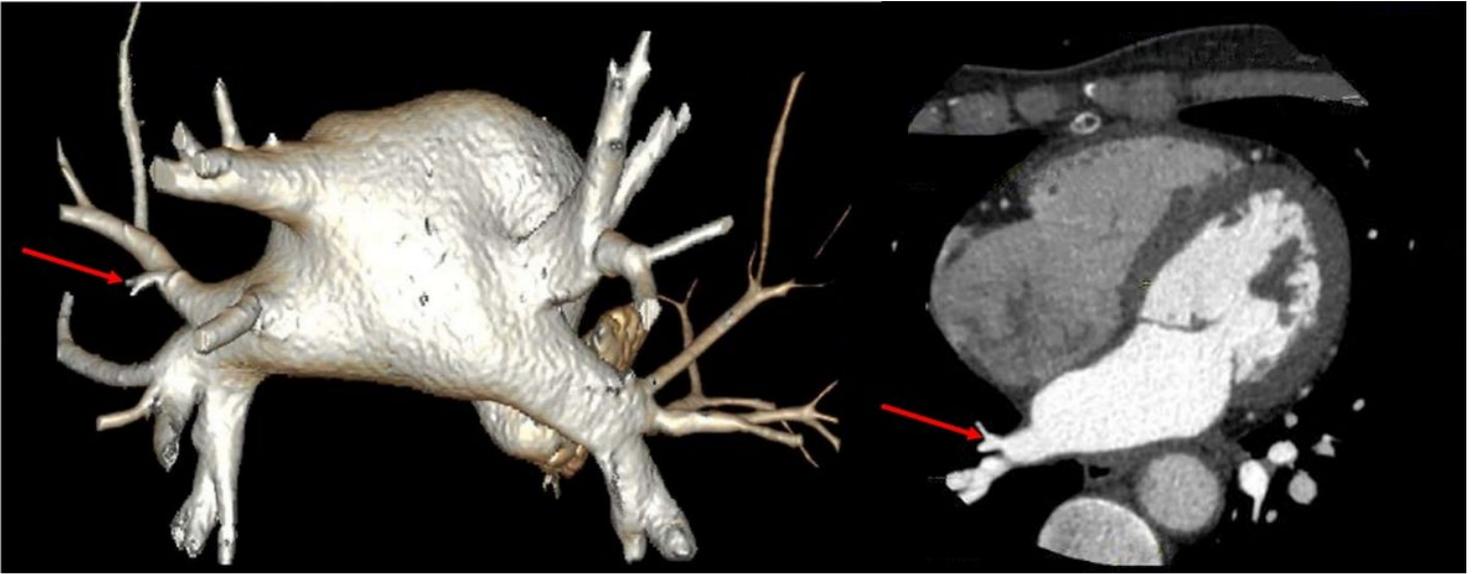


Figure2. CTA of left atria-pulmonary vein showed the middle branch of the right pulmonary vein was variable

Figure 2

Figure 2

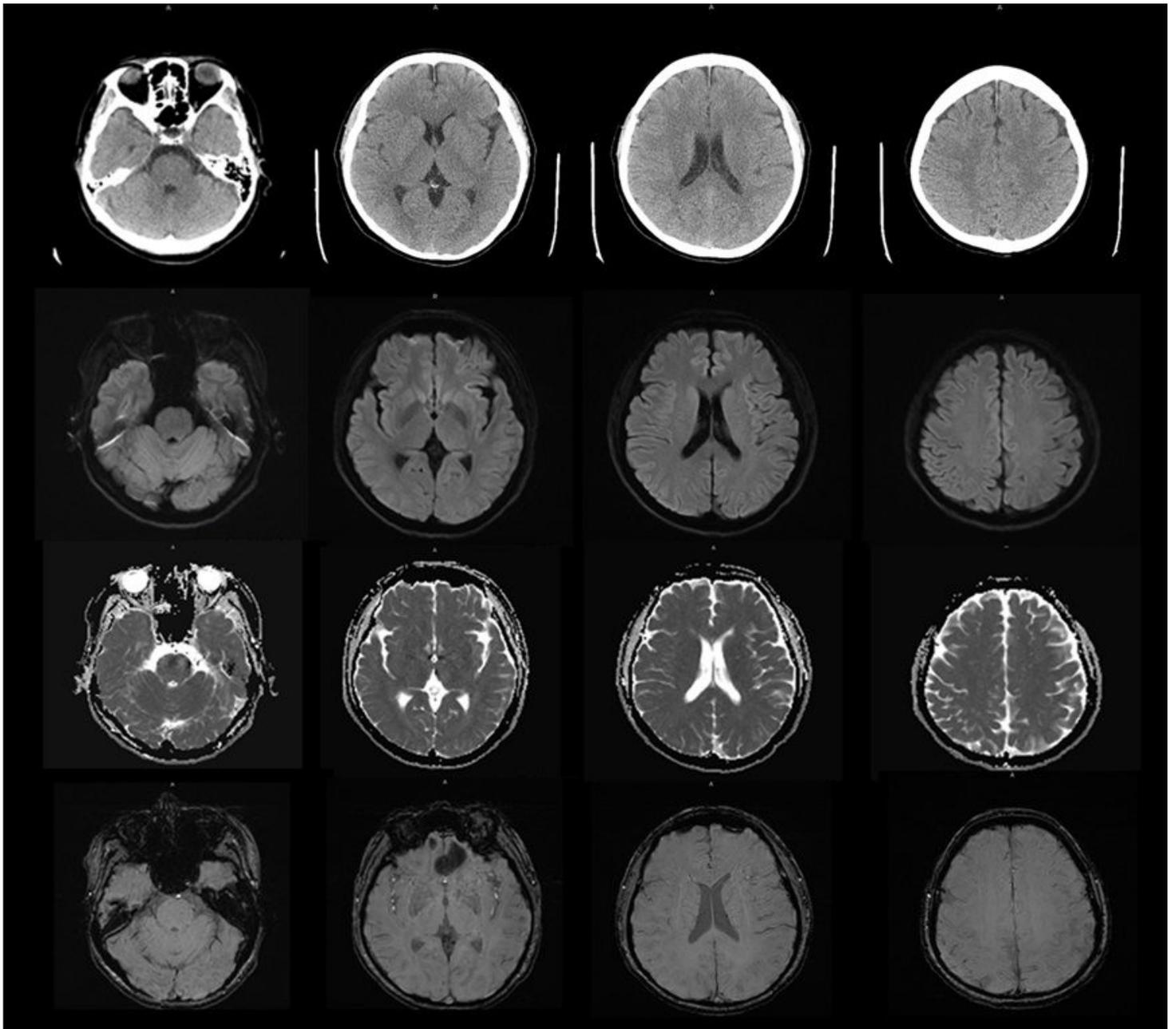


Figure 3 . Head CT and MRI (DWI/ADC/SWI) showed no abnormal signal.

Figure 3

Figure 3

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