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Case Presentation
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Safety of Post-Dabigatran, Non-Antidoted Intravenous Thrombolysis for Acute Ischemic Stroke

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Abstract

Dabigatran is one of the novel oral anticoagulants for stroke prevention in people with atrial fibrillation. Although the presence of antidote, availability, and feasibility are still challenging issues. At present, there is no conclusive recommendation regarding the post-dabigatran, non-antidoted intravenous thrombolysis for acute stroke patients. We presented a case of safely application of intravenous thrombolysis to a post-dabigatran, non-antidoted, 84-year-old female with acute non-large artery ischemic stroke.

Keywords: Dabigatran; Antidote; Thrombolysis; Stroke

Abbreviations

NIHSS: National Institute of Health Stroke Scale; CT: Computed Tomography; AF: Atrial Fibrillation; AIS: Acute Ischemic Stroke; NOAC: Novel Oral Anticoagulant; rt-PA: recombinant tissue Plasminogen Activator; LVO: Large Vessel Occlusion; TT: Thrombin Time; aPTT: activated Partial Thromboplastin Time; ICH: Intracranial Hemorrhage; INR: International Normalized Ratio

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Background

Atrial Fibrillation (AF) patients have five times higher risk of ischemic stroke than non-AF patients [1]. Dabigatran is a Novel Oral Anticoagulant (NOAC) widely used for ischemic stroke prevention upon AF. Acute Ischemic Stroke (AIS) patients with the prescription of dabigatran are recommended to use antidote prior to receiving intravenous thrombolysis with recombinant tissue Plasminogen Activator (rt-PA) [2,3]. However, the antidote of dabigatran, idarucizumab, is not always available immediately in every hospital and the transferring of AIS patients for the administration of antidote is time-consuming. Treatment of AIS with rt-PA is of proven benefit for select patients given up to 4.5 h after symptom onset [4,5].

Therefore, non-antidoted intravenous rt-PA therapy is the sole possible solution for post-dabigatran AIS patients without LVO evidence.

Thrombin Time (TT) is a good indicator of the anticoagulant activity of dabigatran. It was reported that intravenous rt-PA might be safe in LVO-related AIS patients with normal activated Partial Thromboplastin Time (aPTT) and more than 10 h after the last dose dabigatran [6].

Case Presentation

The 84-year-old female had a history of AF and prescribed dabigatran 110 mg irregularly around twice a day. She was witnessed with acute onset of right limbs weakness, right central facial palsy, and slurred speech while praying with neighbors at 10:30 am. The last dabigatran prescription was 3 h before the onset of the stroke. At the emergency room, the initial National Institute of Health Stroke Scale (NIHSS) was 12 at 12:08 pm. neurological examination did not disclose LVO evidence including eye balls deviation, aphasia or conscious disturbance. The patient was fulfilled most of the criteria of intravenous thrombolysis with rt-PA, including the negative of ICH by brain Computer Tomography (CT), normal prothrombin time (10.9 sec), activated Partial Thromboplastin Time (aPTT) (31.7 sec), International Normalized Ratio (INR) (1.04),

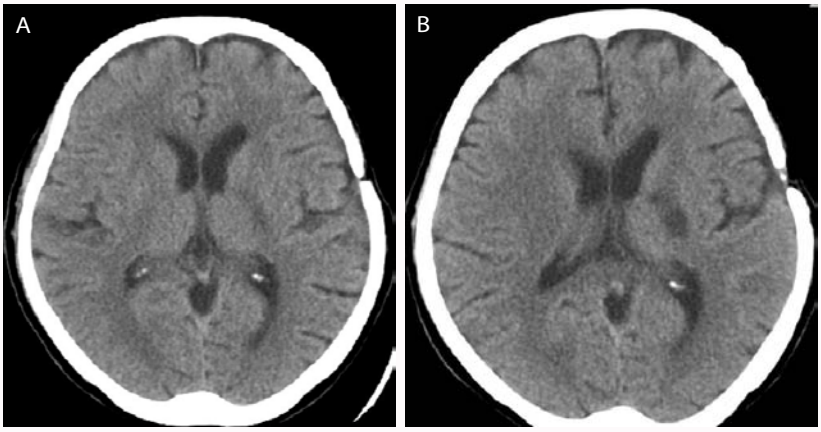

Figure 1: The brain computer tomography 1-day and 7-day after the intravenous thrombolysis treatment with rt-PA:
1A) Brain CT 1-day after the treatment showed left internal capsule hypodensity lesion without hemorrhage transformation.
1B) Brain CT 7-day after the treatment showed enlarged of cerebral infarction over left hemisphere.

platelet count (181 k/mL), alanine aminotransferase (6 U/L) and estimated glomerular filtration rate (63 mL/min/1.73m^2). However, the exact history of dabigatran's prescription and the unavailable antidote of dabigatran, idarucizumab, immediately contraindicated to the intravenous thrombolysis treatment. Clinically, mechanical thrombectomy was unnecessary, based on the impression of non-LVO AIS. After thoughtful discussion with her family, the risks and benefits of intravenous r-tPA in such a unique condition were understood, and rt-PA (0.6 mg/kg) was applied (12:19 pm.) and following NIHSS improved to 4 one hour after completed loading of rt-PA.

The post-rt-PA brain CT was done in the other day, twenty-two hours after treatment, which revealed an acute cerebral infarction at the left internal capsule without hemorrhagic transformation (Figure 1A). However, her NIHSS deteriorated to 9 at forty-eight hours after treatment, which presented as worsening of right-side weakness without disturbance of consciousness or language dysfunction. Repeated non-contrast brain CT at 7-day after treatment revealed an enlarged infarction area compared with the first CT (Figure 1B). After three months of following-up, she can finally walk by herself and enjoy the clear speech, and the modified Rankin scale improved from 5 to 3 and NIHSS improved to 6. The family and patient were satisfied with the treatment outcome.

Discussion

In the latest AIS management guideline, it is not well established about the safety of intravenous thrombolysis with rt-PA for people with prior prescriptions of dabigatran or other NOACs [7]. It had been reported that a left middle cerebral artery occlusion patient who was on dabigatran with normal aPTT might be safe to receive intravenous rt-PA after more than 10 h from the last dose of dabigatran. Only petechial hemorrhage was complicated, and the clinical improvement was remarkable. Certainly, AIS patients with large vessel occlusion on dabigatran within 48 h were recommended to undergo mechanical thrombectomy directly at unavailable antidote conditions as an alternative to recanalize the occlusive vessel. Nevertheless, for AIS patients on dabigatran without available quick antidote who suffer from small to medium vessel size infarction, there is no concrete instruction to disclose the safety of receiving intravenous rt-PA.

It used to be the case that patients effectively anticoagulated with dabigatran were contraindicated for thrombolytic therapy until the ability to rapidly reverse the anticoagulant activity of dabigatran with idarucizumab [8]. However, AIS patients on dabigatran are not always rapidly available to reverse with idarucizumab for scarcity. For AIS patients on dabigatran without necessary thrombectomy, unavailable rapid antidote use, and no establishment of thrombin time, intravenous rt-PA is the sole possible reperfusion manner recanalize the occluded vessels.

It had been a survey of US stroke specialists in 2012. Among 221 vascular neurologists, nearly half of them would not treat AIS patients eligible for intravenous r-tPA under the prescription of dabigatran (time of last dose unknown). In contrast, more than one-quarter consider r-tPA regardless of aPTT, and 28% would treat if aPTT were normal. There were 9% of vascular neurologists would treat if aPTT was less than 40 sec, and 4% would treat regardless of aPTT [9]. Thus, a remarkable lack of consensus among vascular neurologists regarding the assessment and treatment of acute stroke patients on dabigatran, even with normal aPTT lab profile. Some article regards the combination of two normal lab profiles (TT and aPTT) without other contraindication as a safety assessment for AIS patients on dabigatran eligible IV r-tPA or not [10].

From the hematology points of view, aPTT and TT play significantly different roles. A normal aPTT excludes the above on-therapy levels of dabigatran but does not exclude the presence of dabigatran in the on-therapy range; Normal Thrombin Time (TT) excludes the presence of dabigatran. A prolonged TT could suggest either the presence of clinically relevant or trivial levels of dabigatran. Therefore, without the support of a normal TT lab profile, normal aPTT suggests at least no evidence of excessive dabigatran, which also means relatively safe even on concurrent dabigatran use [11]. Although TT is a better lab profile concerning safety than aPTT; it not available to obtain in the community-based hospital immediately, for now, is its shortcoming. In our case, normal aPTT without other contraindication might suggest relative safety for eligible IV r-tPA therapy.

A pragmatic approach for the management of patients with AIS while taking dabigatran was suggested. First of all, obtaining information on the nearest dosage and time of prescription. Second, obtaining information on comorbidity and concomitant medication and collecting lab tests (coagulation test, aPTT; renal function,

platelet count). Finally, after a multidisciplinary assessment of risks and benefits, a favorable profile (low bleeding risk, severe disable deficits) is fulfilled, intravenous rt-PA should be considered [12]. It was recently reviewed that prior intake of NOAC within 48 h of intravenous rt-PA bolus was not associated with an increased risk of symptomatic hemorrhagic transformation in selected AIS patients [13].

Conclusion

The present study reported a successful intravenous rt-PA treatment of AIS for a patient on dabigatran without reversal antidote. Further studies should be conducted to prove intravenous rt-PA therapy's safety in AIS patients with normal aPTT on dabigatran use within hours. The short interval between the latest dabigatran dose with the onset of stroke hours might not be the sole reason to exclude early management in acute stroke patients without evidence of large vessel occlusion.

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