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Case Report

Successful intravenous thrombolysis in a patient with ischemic stroke, after reversal of Dabigatran with Idarucizumab – A case report

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ABSTRACT

There remains a risk of ischemic strokes in patients of atrial fibrillation receiving oral anticoagulants. Systemic thrombolysis in such cases poses a challenge, but may be possible after reversal of anticoagulant effect. We report a case of 61-year old male patient with non-valvular atrial fibrillation who was taking dabigatran. The patient developed ischemic stroke few hours after taking the last dose of the anticoagulant. Reversal of dabigatran was achieved using idarucizumab, and the patient was successfully thrombolysed. This case-report adds to the growing evidence that such a strategy is now possible with the advent of reversal agents against non-vitamin K antagonist oral anticoagulants.

1. Introduction

Patients with atrial fibrillation (AF) are at an increased risk of ischemic strokes. Oral anticoagulants (OACs) are frequently used in such patients to reduce this risk. Until around a decade ago, vitamin K antagonists were the mainstay. However, currently non-vitamin K antagonist oral anticoagulants (NOACs) are recommended over vitamin K antagonists in patients who are eligible for NOACs. Dabigatran 150 mg b.i.d. has shown superiority over well-controlled warfarin in reducing the risk of ischemic stroke in patients with non-valvular atrial fibrillation.[1] Yet, there would be some patients who present with an ischemic stroke despite prophylactic anticoagulation.

Alteplase is a standard therapy for patients of ischemic stroke who are eligible for thrombolysis, and is recommended by various guidelines.[2,3] Anticoagulation is considered to be a relative contraindication for thrombolysis, and the benefits of thrombolysis must be weighed against increased risk of bleeding.[2,4] Management of stroke is such, anticoagulated patients, therefore, becomes challenging.

Following its approval in the United States of America (USA) in 2015, idarucizumab (Praxbind) was approved in India in 2017. It is a humanized monoclonal antibody fragment specific to dabigatran, and was tested in the RE-VERSE AD trial, in two groups of patients – patients who suffered uncontrolled or life-threatening bleeding, and patients who required an urgent surgery or invasive procedure for which normal hemostasis was required.[5] It was observed that idarucizumab resulted in a rapid (within minutes) and complete reversal of dabigatran in more than 98% percent of patients who had a prolonged diluted thrombin time (dTT) at baseline. Reversal was independent of age, sex, renal function, and dabigatran concentration at baseline. Reversal based on activated partial-thromboplastin time (aPTT) or thrombin time (TT) was similar to that based on dTT. Importantly, Idarucizumab has not shown any pro-thrombotic effect in animals or healthy human volunteers.

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Extensive data on systemic thrombolysis in anticoagulated patients presenting with ischemic stroke are lacking. However, reversal of anticoagulant effect may allow thrombolysis in such patients who otherwise could not have been thrombolysed. We report such a case of successful thrombolysis after reversal of anticoagulation, in a patient of ischemic stroke who was receiving dabigatran.

2. Case Report

A 61-year-old male patient presented to our hospital on 12^{th} April 2019 at around 0930 h, within an hour of onset of sudden right-sided weakness with facial deviation and drooling of saliva. The patient had experienced an episode of CVA in 2016 following which the patient had shown complete recovery. The patient was a known case of hypertension and hyperlipidaemia and was on treatment with telmisartan 40 mg o.d. and rosuvastatin 10 mg o.d. He was a known case of atrial fibrillation since 4 years and was on treatment with dabigatran 150 mg twice daily.

Laboratory investigations were evaluated and aPTT was observed to be deranged (>120 seconds). Rest of the laboratory parameters did not demonstrate any significant abnormality. Neurological examination revealed Broca's aphasia, right sided faciobrachial weakness in the form of right-sided upper motor neuron palsy. NIHSS was 10.

A non-contrast CT scan showed no signs of bleeding. MRI of the brain was done to evaluate the extent of infarct. The findings suggested multiple acute-subacute non-hemorrhagic infarcts in the left centrum semiovale, corona radiata and the parietal lobe involving the cortex and subcortical white matter. A CT angiography was done which did not depict any obvious abnormality. A diagnosis of acute left MCA territory stroke was made and decision was made to thrombolyse the patient using Injection Alteplase.

Since the aPTT was high and the patient mentioned that the last dose of dabigatran was taken in the morning of the day of the event, decision was taken to administer Idarucizumab (Praxbind), a specific reversal agent of dabigatran etexilate, prior to thrombolysing the patient. The patient was administered 5g of Injection Praxbind as an IV bolus injection. Within 40 minutes of Praxbind administration, the patient was thrombolysed using 50 mg of IV alteplase (5 mg as a bolus dose followed by the 45 mg IV infusion over the next one hour). The patient was monitored in the intensive care unit for the next two days. Improvement in power and speech was observed. The patient was shifted out of the ICU on day 3. On day 5 post-thrombolysis, decision was taken to discharge the patient as the vitals were stable and patient was functionally independent. At discharge, Pradaxa 150 mg twice daily was restarted along with the regular medicines and tablet Ecosprin 75 mg was added to therapy. Subsequent follow-ups did not show any residual abnormality or signs of a residual CVA.

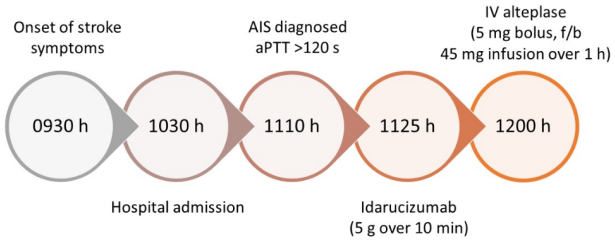

Fig. 1: Timeline, from symptom-onset to thrombolysis.

3. Discussion

To the best of our knowledge, this is the second published report from India, wherein intravenous thrombolysis was successfully performed after reversal of the effect of Dabigatran.

EHRA practical guide[6] mentions that the use of thrombolysis for acute ischemic stroke cannot be recommended in situations where the anticoagulation status of the patient is unknown or when the last intake of an NOAC is within the last 24 h (or even longer in case of renal insufficiency). However, for dabigatran, availability of reversal agent provides an opportunity for thrombolysis even if these criteria are not met.

Rapid testing of plasma NOAC level and specific coagulation assays (dTT/ECT for Dabigatran or anti-FXa assay for Apixaban/Rivaroxaban) can provide indication about the anticoagulation status of the patient. Unfortunately, these tests are not widely available in India. For Dabigatran, aPTT can also provide useful information, although it is not as useful as dTT/ECT. The relationship between aPTT and Dabigatran is curvilinear. So, while aPTT in the normal range does not exclude therapeutic effect of Dabigatran, above-normal aPTT does indicate dabigatran's anticoagulant effect. Our patient had taken the last dose of dabigatran just a couple of hours before onset of symptoms, and aPTT was also raised above normal. Hence, thrombolysis could not have been done without first reversing the effect of the anticoagulant.

Timing of re-initiation of anticoagulation therapy after an acute ischemic stroke is based on consensus opinion, and should take into consideration the risk of haemorrhagic transformation and the risk of recurrent stroke. In our patient, dabigatran was re-instituted at discharge, five days after stroke. There were no haemorrhagic complications on follow-up.

4. Conclusion

This report adds to the growing evidence that reversal of dabigatran with Idarucizumab before thrombolysis may be considered for patients who suffer an ischemic stroke while receiving dabigatran. Further evidence supporting this strategy is desirable. While OACs significantly reduce the

risk of ischemic stroke in patients with atrial fibrillation, some risk of stroke still remains. Thrombolysis in such patients poses a clinical dilemma because effective anticoagulation is a contraindication to thrombolysis. Availability of a reversal agent is an important development as it may allow thrombolysis in such patients.

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6. Conflict of Interest

The authors declare they have no conflict of interest.

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