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Case Report

Ischemic stroke following reversal of dabigatran with idarucizumab in spontaneous subdural hematoma in cerebral venous thrombosis

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ABSTRACT

Spontaneous subdural hematomas (SDH) are an unusual but potentially devastating complication of oral anticoagulation. Emergency management of subdural hematomas following oral anticoagulant therapy consists of reversal of anticoagulation coupled with surgical evacuation, if indicated. However, the question of reintroducing anticoagulants is a conundrum faced by clinicians. Clinical equipoise remains divergent among neurologists and literature guiding them is sparse. We report a case of spontaneous acute SDH in a middle-aged woman receiving dabigatran for cerebral venous thrombosis (CVT). Dabigatran reversal was achieved with idarucizumab and burr hole evacuation of the SDH was performed successfully. However, the patient suffered left posterior cerebral artery (PCA) territory ischemic stroke during this period, which appears to be a result of reversal of anticoagulant effect of dabigatran by idarucizumab. With this case report, we seek to highlight this rare complication of dabigatran therapy in CVT, the effectiveness of idarucizumab in reversing dabigatran action and the risks of interruption of dabigatran therapy with idarucizumab.

Keywords: Cerebral venous thrombosis, Dabigatran, Idarucizumab, Spontaneous subdural hematoma, Subdural hematoma, Ischaemic stroke

INTRODUCTION

Dabigatran is a non-vitamin K antagonist directly acting oral anticoagulant (DOAC) of the direct thrombin inhibitor class of drugs. Dabigatran was the first DOAC to be approved by the United States Food and Drug Administration (FDA) and is indicated in the primary and secondary prophylaxis of different thromboembolic states including stroke prevention in non-valvular atrial fibrillation (AF) and venous thromboembolism (VTE).[1] It has been shown to be non-inferior to Warfarin in the treatment of cerebral venous thrombosis (CVT) and is being increasingly preferred due to its favourable safety profile and lack of need for scrupulous monitoring. Subdural hematomas are an unusual but potentially devastating bleeding complication in those on dabigatran and other anticoagulants. Idarucizumab is a humanized monoclonal antibody developed as a specific reversal agent for dabigatran.

Approved by the US FDA in 2015, it is indicated for the rapid reversal of anticoagulant effect in patients on dabigatran therapy slated to undergo emergency surgeries or in life threatening, uncontrolled bleeding.[2] The question of reintroducing anticoagulation in such patients is a clinical dilemma among neurologists with no clear consensus or guidelines.

CASE REPORT

An apparently healthy 52-year-old lady presented to our emergency department with complaints of new onset headache in the right occipital region which was continuous, severe in intensity and unaffected by changes in posture. There was no history of fever, vomiting, seizures, altered sensorium, weakness of limbs, blurred vision, dysarthria, dysphagia or consumption of oral contraceptive pills. Her vital parameters and neurological examination were normal. A magnetic resonance imaging (MRI) scan of brain with venography (MRV) showed absent flow related enhancement with blooming of superior sagittal sinus, right sigmoid sinus, right transverse sinus, internal jugular vein and superficial cortical veins suggestive of cerebral venous thrombosis. (Figure 1). Blood investigations revealed mild anaemia (Hb-10.3 g/dl). Pro-coagulant work-up was negative.

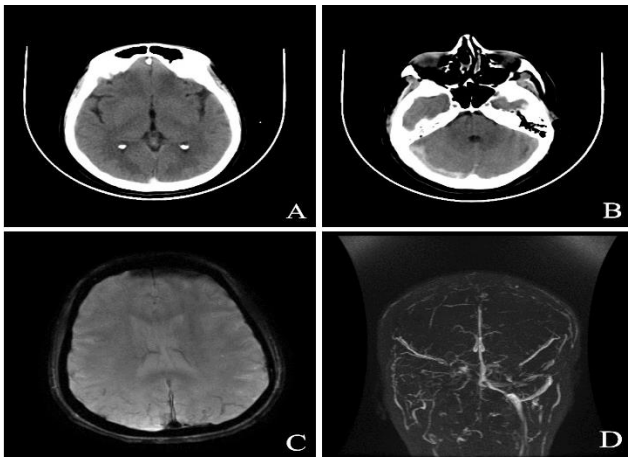

Figure 1: (A) Non enhanced CT (NCCT) brain, axial section showing hyperdense posterior superior sagittal sinus; (B) NCCT brain, axial section showing hyperdense thrombus in the right transverse sinus; (C) MRI brain, susceptibility weighted imaging (SWI) sequence, axial section showing increased susceptibility signals within the posterior part of the superior sagittal sinus; and (D) phase contrast MRV, reconstructed image showing thrombosis of superior sagittal sinus, bilateral transverse sinus, right sigmoid sinus and internal jugular vein.

She was initiated on anticoagulation with enoxaparin and changed to dabigatran 150 mg twice daily at the time of discharge. She was symptomatically better at discharge and had no neurological deficits. Two weeks later she again presented to the emergency department with continuous holocranial headache of one-day duration, increasing in severity and associated with multiple episodes of vomiting. Neurological examination was normal. MRI of brain showed interval development of left fronto-temporo-parietal acute subdural hematoma causing mass effect and midline shift of 11 mm to the right with left uncal herniation (Figure 2). As her thrombin time was prolonged (test-83 sec, control-21 sec), we administered 2 vials of 2.5 gm of idarucizumab as intravenous bolus and she was taken up for burr hole evacuation of the left sided SDH. Repeat thrombin time done post-surgery, 4 hours after administration of idarucizumab was 18.8 sec (control 21.3 sec). On the first post-operative day she complained of diminished vision in her right hemifield. Examination confirmed right hemianopia. An MRI brain was repeated which showed diffusion restriction in the left occipito-temporal lobe suggestive of subacute PCA territory infarcts, along with satisfactory clearance of the left fronto-temporo-parietal SDH (Figure 3). She was started on apixaban 5 mg twice daily 2 weeks after her surgery and was continued for 6 months. She had no further bleeding or thrombotic complications during this period and only mild improvement was noted in visual field defect at 7-months follow up.

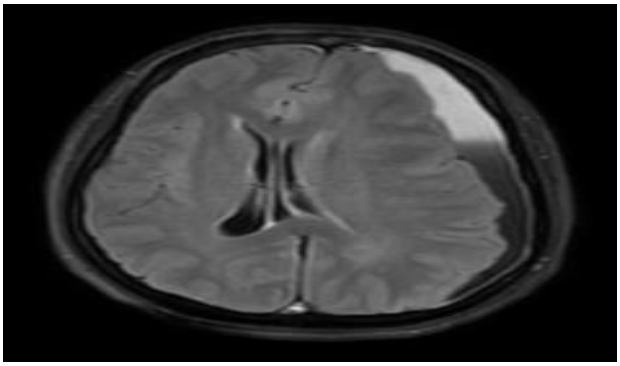

Figure 2: MRI brain, T2 FLAIR sequence, axial section showing acute subdural hematoma along left cerebral convexity with internal fluid levels.

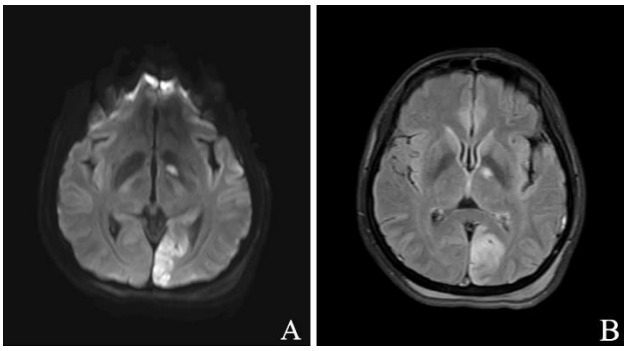

Figure 3: (A) MRI brain, diffusion weighted imaging (DWI), axial section showing restriction in left medial occipitotemporal lobe and medial globus pallidum suggesting left posterior cerebral artery territory infarct; and (B) MRI brain T2 FLAIR sequence, axial section showing hyperintensity in the same areas confirming subacute infarcts.

DISCUSSION

Dabigatran and other DOACs, are highly efficacious anticoagulants. They have minimal drug-drug and drug-food interactions, are non-inferior compared to warfarin

and do not, in most cases, require scrupulous monitoring of INR. Studies that compare risk of bleeding in different classes of anticoagulants report similar results favouring DOACs over VKA's.[3,4] The RE-COVER study of 2564 enrolled patients, found dabigatran to be comparable to Warfarin for the prevention of recurrent venous thromboembolism (VTE) (2.4% versus 2.1%).[3] The incidence of major bleeding was marginally lesser in those on Dabigatran (1.6% versus 1.9%). Another large randomised control trial (RE LY) on 18,113 patients with atrial fibrillation and risk of stroke concluded that dabigatran at a dose of 110 mg twice daily was associated with rates of stroke and systemic embolism similar to those associated with Warfarin but with lower rates of major haemorrhage, while dabigatran administered at a dose of 150 mg twice daily was associated with lower rates of stroke and systemic embolism but similar rates of major haemorrhage compared with Warfarin.[4] The results of the RE LY trial has played a pivotal part in the mainstream acceptance of this drug.

Intracranial haemorrhages (ICH) are a significant and devastating consequence in those on oral anticoagulants. While traumatic ICH following injury to bridging veins in anticoagulated patients is well-known, spontaneous ICH, specifically spontaneous acute SDH, is an unusual complication in those on anticoagulant therapy. It would be worthwhile to note that while both cohorts seem to benefit from restarting anticoagulation, spontaneous ICH seems to have a higher rebleeding and lower or equal thrombotic risk.[5] The mortality rates of anticoagulant related acute SDH in recent series is between 13% to 20%, underlining the gravity of this complication.[6] One study found that oral anticoagulant therapy increased the risk of SDH 4 to 15-fold with the rate being influenced by factors such as duration and intensity of anticoagulation and patient factors such as advanced age.[7]

Clinicians face a conundrum when reintroducing anticoagulants in patients that have had an anticoagulant associated ICH. Risk of expansion of hematoma and/or new haemorrhagic lesions coupled with scant literature guiding re-initiation influences decisions. Recent literature suggests that the benefit of restarting anticoagulation and thus preventing thrombotic events outweighs risk of rebleed in most situations.[5,6] One study of the outcome of 49 patients who suffered SDH while on oral anticoagulants reported that thromboembolic events occurred in 4/23 patients who were not restarted on anticoagulation versus 0/15 patients restarted on phenprocoumon (VKA); haemorrhagic complications occurred in 1/23 uncoagulated versus 0/15 recoagulated patients.[6] With DOACs having a lesser risk of ICH compared to VKAs, the benefit of restarting is likely more.

A Canadian study on the trends in reinitiating anticoagulation after surgical evacuation of SDH among neurosurgeons and neurologists found that 36% restarted within 1 week of surgery, 44% between week 1 and week 4 and 19% after 4 weeks reflecting variation between practitioners.[8] In the current scenario, further large scale randomized controlled trials probing this aspect are warranted. There are few case reports of SDH following initiation of dabigatran therapy in patients with stroke and atrial fibrillation in the literature. In our experience, this is the first case of spontaneous SDH following dabigatran therapy for CVT. The aforementioned cases were successfully treated with idarucizumab followed by burr hole evacuation.[9]

The first step in management is to discontinue dabigatran. Evidence of dabigatran anticoagulation is based on clinical history of ingestion within 3.5 days and laboratory evidence (elevated TT, aPTT, dTT, and Ecarin clotting time). Reversal is achieved by administering 5 g idarucizumab as an intravenous bolus.[10] Administration of clotting factor products like activated prothrombin complex concentrate (aPCC) at a dose of 50-80 units/kg is an alternative. Earlier, lack of a specific antidote for the reversal of dabigatran was a source of hesitation for physicians prescribing it. Idarucizumab, a humanized monoclonal antibody, was developed as a specific, rapid (within minutes) reversal agent for dabigatran. The reversal of dabigatran by idarucizumab can be assessed by monitoring the anticoagulant profile or measuring dabigatran plasma concentrations before and after administration.[2] Repeat dosing may be indicated in select cases like overdose and persistent prolonged aPTT. Complications of idarucizumab include thrombosis due to underlying thrombotic risk factors in patients.[2,10] A search of the literature on risk of thrombosis following idarucizumab yielded the REVERSE AD study which reported that 29% of individuals (5/17) who did not restart anticoagulation subsequently developed thrombotic events 2 to 26 days after treatment. Of these, 1 developed thrombosis after 48 hours while others after 72 hours.[10] In our patient, thrombotic episode occurred within 12 hours of administering idarucizumab. The development of PCA territory infarct in this case is attributed to idarucizumab and withdrawal of anticoagulant effect of dabigatran. No other thrombotic risk factor was identified in our patient after detailed evaluation. Our experience highlights the efficacy of idarucizumab in reversing dabigatran effect while cautioning us about its prothrombotic effects.

CONCLUSION

Thromboembolic events recurring in patients following reversal of DOACs is a definite risk and further complicates management in inherently complicated cases. The benefits of restarting anticoagulation therapy in patients post SDH is clear with consensus being that DOACs have a lesser risk of haemorrhage compared to VKAs. Clinical equipoise on when to restart, however, remains divergent and non-uniformity among workers persists. Current literature on the same is limited and there is a need for further large scale randomised controlled trials. Where restarting anticoagulants is being considered, a case-by-case approach must be adopted. Risk and benefit

in individual situations must be carefully weighed. In this case, the thrombotic event seemed to be a result of idarucizumab and withdrawal of dabigatran, highlighting the risks of interrupting oral anticoagulants in those that need it most.

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