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Use of novel oral anticoagulants for Treatment of cerebral venous sinus Thrombosis: a case series and follow up

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USE OF NOVEL ORAL ANTICOAGULANTS FOR TREATMENT OF CEREBRAL VENOUS SINUS THROMBOSIS: A CASE SERIES AND FOLLOW UP

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ETHICAL STATEMENT

The authors declare that they do not have any conflict of interest.
Informed consent was obtained from all individual participants.

ABSTRACT

INTRODUCTION

Thrombosis of cerebral venous sinuses and/or cortical veins (CVST) is an infrequent type of stroke for which anticoagulation is considered standard of treatment. However, 40% of CVST patients have evidence of parenchymal changes like edema or haemorrhage on neuroimaging which complicates use of anticoagulation in such cases. Therefore, Novel Oral Anticoagulants (NOACs) are recently being used for treatment of CVST as they are associated with half the risk of intracerebral haemorrhage as caused by vitamin K antagonist. Case reports and case series have reported use of NOACs in CVST with good outcomes both clinically and radiologically. We report use of NOACs in five cases of CVST without any worsening or recurrence of symptoms or complication on follow up.

CASE PRESENTATION

We report five cases of CVST, most of them presented with headache associated with sensorimotor symptoms or seizure. Two patients had cerebral infarction and one of them had hemorrhagic transformation of cerebral infarction. Superior sagittal sinus was most commonly involved sinus. Heparin or Enoxaparin were used as initial therapy. Dabigatran was used as continuation therapy in four patients and Apixaban was used in one case. None of the patients developed worsening or recurrence of symptoms or bleeding complications on follow up.

CONCLUSION

NOACs can be used as a safe and effective alternate of vitamin K antagonist for treatment of CVST.

Keywords: Novel oral anticoagulants, cerebral venous sinus thrombosis, Dabigatran, Apixaban

INTRODUCTION

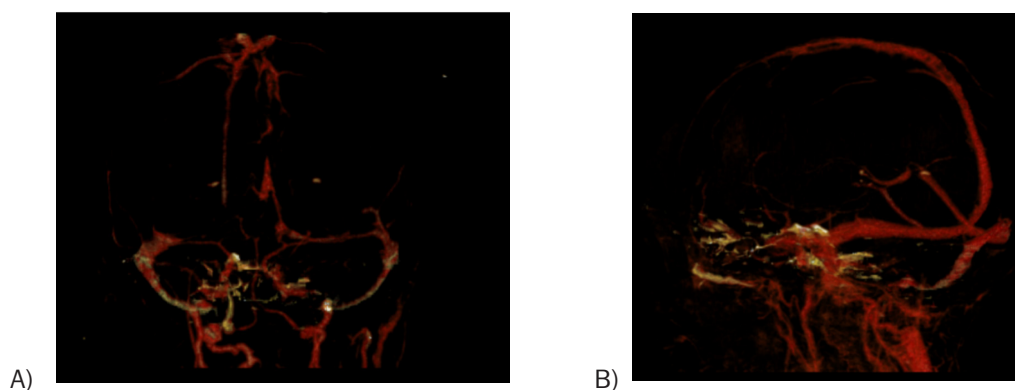
Thrombosis of dural venous sinuses and/or cerebral veins (CVST) accounts for approximately 0.5% to 1% of all strokes usually affecting young individuals. Anticoagulation is gold standard to treat such cases. However, 40% of CVST patients have evidence of edema and haemorrhage on neuroimaging which complicates use of anticoagulation in such cases. Novel Oral Anticoagulants (NOACs) are associated with significantly lower risk of intracranial haemorrhage as

compared to vitamin K antagonists which makes them better alternative for use in cases of CVST. We report five cases of CVST who were treated with NOACs without recurrence of symptoms or bleeding on follow up.

CASE PRESENTATION

Case1:

46 years old lady, married with two children, no known medical illness, presented with headache for 2 weeks followed by 3 episodes of generalized tonic clonic seizures. Her neurologic examination was unremarkable except for papilledema. Noncontrast CT head showed hyperdense superior sagittal sinus and CT venogram showed right transverse sinus and superior sagittal sinus thrombosis. Patient was started on Levetiracetam 500mg twice daily and Enoxaparin for first 7 days then switched to Dabigatran 150mg twice daily. On follow up, she was found to have protein C deficiency. Follow up imaging 8 months later showed complete recanalization of thrombosed sinuses.



A)CT venogram at presentation showing filling defect in right transverse and superior sagittal sinuses and B)repeat CT venogram eight months later showing complete recanalization.

Case 2:

25 years old girl, known case of schizophrenia on Quetiapine, presented with right sided weakness. On examination she had dysarthric speech with right facial palsy and right sided hemiparesis. MRI brain showed left MCA acute infarction with haemorrhagic transformation and MR venogram showed thrombosis of superior sagittal sinus, right transverse sinus, right sigmoid sinus, right internal jugular vein and deep cortical veins.



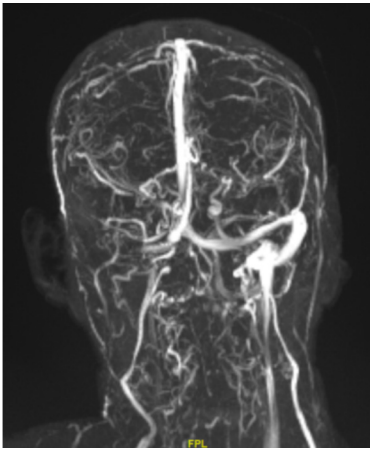
MR venogram showing superior sagittal sinus thrombosis.

She was started on heparin infusion and later on switched to enoxaparin. Enoxaparin was then switched to Dabigatran 150mg twice a day after 2 weeks. Her symptoms improved almost completely and did not develop any recurrence of symptoms or bleeding complication during follow up for 6 months.

CASE 3:

29 years old lady, no known medical illness, presented with headache and blurring of vision followed by numbness of left arm. She was taking oral contraceptive pills at that time. Her neurologic examination showed papilledema and pronator drift in left arm.

MR venogram showed superior sagittal sinus thrombosis. She was started on Enoxaparin then switched to Apixaban 5 milligrams twice daily after one week. Her symptom improved completely and was discharged on Apixaban. She was stable on her follow up without any complication.



MR venogram showing right transverse and sigmoid sinus thrombosis extending into right internal jugular vein.

Case 4:

27 years old gentleman, no previous medical illness, presented with fever, right ear discharge, headache with vomiting and decreased level of consciousness. He had history of recurrent right ear discharge for 6 months. On examination, he was febrile, drowsy but arousable to verbal stimulus with dysarthric speech, partial sixth nerve palsy, nystagmus on both horizontal and vertical gaze. His blood work up showed ESR of 101, CRP of 19.9, white cell count of 18,700 with predominant neutrophils. His head CT with contrast showed communicating hydrocephalus and subdural collection along right cerebellar hemisphere with mass effect. MRI head and MRV head showed right otomastoiditis with adjacent subdural empyema and right transverse sinus, right sigmoid sinus and right internal jugular vein thrombosis.

He underwent insertion of external ventricular drain along with drainage of subdural abscess and right mastoidectomy. He was started on heparin infusion and parenteral antibiotics. His heparin infusion was switched to enoxaparin then Dabigatran 150 milligrams twice daily was started. He was discharged in stable condition. Dabigatran was discontinued after 6 months. Upon his follow up in clinic, he did not have any new deficit or bleeding complication.

CASE 5:

47 years old lady, no previous medical illness, was hospitalized for investigation of anemia. During her hospitalization, she developed headache with right sided weakness and difficulty speaking. On examination she had dysarthric speech with right facial palsy and right sided hemiparesis. Non contrast CT head showed ischemic infarction of left frontal lobe and CT venogram showed thrombosis of superior sagittal sinus, left transverse sinus and left internal jugular vein. She was diagnosed with iron deficiency anemia and was transfused packed Red Blood Cells and her haemoglobin remained stable later on. She was started on heparin infusion initially then switched to enoxaparin after 3 days. Enoxaparin was switched to dabigatran 150mg twice daily after one week. She recovered completely over 2 days. She did not have recurrence of symptoms or bleeding complication on follow up.

DISCUSSION:

Thrombosis of dural sinus and/or cerebral veins (CVST) accounts for approximately 0.5% to 1% of all strokes usually affecting young individuals.^{1,2} According to the International Study on Cerebral Venous and Dural Sinuses Thrombosis (ICVST) nearly 80% of patients were less than 50 years of age³. Many predisposing factors have been identified for CVST including thrombophilic conditions, pregnancy and peripartum, oral contraceptives and other medications, inflammatory bowel disease and head trauma to name a few. Diagnosis of CVST is challenging due to diverse presentations. Anticoagulation is standard of care in cases of CVST to prevent thrombus growth as well as to facilitate recanalization. But this approach is complicated by the fact that many cases of CVST have cerebral infarctions with hemorrhagic transformation. Focal parenchymal changes with edema and hemorrhage may be identified in up to 40% of patients⁴. Novel Oral Anticoagulants (NOACs) have been approved for secondary prevention of stroke in cases of atrial fibrillation and also for prevention and treatment of DVT however there is paucity of data on use of NOACs in CVST. Based on limited data on use of anticoagulation in CVST it appears safe and effective. Low Molecular Weight Heparin and Vitamin K Antagonist (VKA) have been used to treat cases of CVST till now but case reports and case series have been published reporting use of NOACs for treatment of CVST. NOACs appear to be safe and effective and have advantage of lower risk of intracranial hemorrhage as compared to warfarin especially in scenario of venous infarctions with hemorrhagic transformation. Hon et al have reported use of Dabigatran for CVST in two patients. One patient had superior sagittal sinus thrombosis and other had left transverse sinus thrombosis. Both were treated with Dabigatran 100mg twice daily for 6 months and showed complete recovery of symptoms as well as resolution of thrombus on follow up scan. There were no bleeding complications⁵. In another study, Rivaroxaban was compared to vitamin K antagonist for treatment of CVST. Seven of 16 patients included in study received rivaroxaban. There were no differences in clinical benefit seen between two treatment groups⁶. Marcelo et al have reported use of dabigatran

in 15 patients with CVST. Excellent outcome defined as grade 0 or 1 on modified Rankin scale was observed in 87% patients at six month follow up, no fatality or CVST recurrence at follow up of 19 months and partial or complete recanalization was seen in 80% at five months⁷. Rao et al have reported use of Apixaban for long term treatment of their 3 cases with CVST, all three had intracranial haemorrhage, none of them developed neurologic deterioration or increase in size of haemorrhage while one patient had complete recanalization on follow up and two had partial recanalization⁸. Ima A Kusuma reported use of Rivaroxaban in a 37 years old lady with left transverse sinus thrombosis who improved without any complications on follow up⁹. Rivaroxaban was also reported to be used for treatment of CVST in two patients without any complication or recurrence and with partial recanalization on follow up¹⁰. Anticoli et al reported use of Rivaroxaban for treatment of CVST in 6 patients. All patients had modified Rankin Scale score 0 to 1 at 3 months follow up and 67% had complete or partial recanalization and none developed any bleeding complication¹¹. In a questionnaire based survey Thaila et al reported that NOACs were used for initial treatment of CVST by 6% of practitioners whereas one third used NOACs for maintenance therapy¹². The Efficacy and Safety of Oral Dabigatran Etxilate Versus Warfarin in Patients with Cerebral Venous and Dural Sinus Thrombosis (RE-SPECT) is investigating efficacy and safety of dabigatran etexilate versus dose-adjusted warfarin on net clinical benefit endpoint of major bleeding and thrombotic events in patients of cerebral venous sinus thrombosis.

Our patient's ages ranged from 25 to 47 years. Patients presented with headache (4 out of 5), motor symptoms (3 out of 5), sensory symptoms, visual symptoms and decreased level of consciousness (each 1 out of 5) and seizures in one. Superior sagittal sinus was most frequently involved sinus followed by transverse sinus and internal jugular vein and deep cortical veins in sequence of decreasing frequency. Two patients had infarction on brain imaging and one of them had hemorrhagic transformation of cerebral infarction. One patient had CVST as complication of otomastoiditis, one had protein C deficiency and one had history of OCP use. Patients were initially treated with heparin infusion in 3 cases and with enoxaparin in remaining two cases. Dabigatran was used for maintenance therapy in four cases whereas Apixaban was chosen in one case. Repeat CT venogram was done in one case and it showed complete recanalization of sinuses. None of patients developed recurrence of symptoms or bleeding complications on follow up.

CONCLUSION:

CVST is an infrequent type of stroke which can have fatal outcome if diagnosed or treated late. Anticoagulation is considered standard treatment of CVST. However, more than one third of CVST patients have signs of edema or haemorrhage on brain imaging which complicates use of anticoagulation in such scenario. NOACs are attractive option in that case as their use is associated with nearly 50% lower risk of intracerebral haemorrhage as compared to vitamin K antagonists. We report use of NOACs in five patients with CSVST without any complication or recurrence of symptoms on follow up. Currently this option of treatment is being evaluated in trials and needs long term follow up as well.

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Rizwana Shahid; concept, data collection, data analysis, manuscript writing, manuscript review

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Aishah Albakr; concept, data collection, data analysis, manuscript writing, manuscript review

Norah Abdulaziz AlKhalidi; concept, data collection, data analysis, manuscript writing, manuscript review

Feras Abdulsalam Abdullah Alsulaiman;

concept, data collection, data analysis, manuscript writing, manuscript review