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Long-term Anticoagulation with Apixaban in Patients with Cerebral Venous Thrombosis

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Abstract

Introduction: Cerebral venous thrombosis (CVT) is a life-threatening neurological condition. There is limited evidence for the use of direct oral anticoagulants (DOAC) for long-term anticoagulation in this patient population. We report a case series of patients treated with apixaban and their clinical course. **Methods:** This was a retrospective cohort study. Patients diagnosed with CVT in a defined time period at our institution were screened for long-term anticoagulation and patients who were treated with apixaban were included in this study. **Results:** A total of nine patients were included in this study. The mean age was 36 years and 56% of the patients included were women. All received initial anticoagulation with unfractionated heparin (UFH) infusion for at least twenty-four hours, except for one patient who had anti-thrombin III deficiency and was treated with argatroban infusion. For long-term anticoagulation, 56% of patients received apixaban 10 mg twice daily for the first five to seven days followed by 5 mg twice daily, while the remaining 44% were transitioned from IV anticoagulation to apixaban 5 mg twice daily. There were no adverse events reported, except for one patient who developed anemia after 7 months of treatment and required a blood transfusion. Complete recanalization was achieved in 78% while 22% had partial recanalization. Follow-up time ranged from six to twenty-three months. **Conclusion:** The use of apixaban for long-term anticoagulation in CVT resulted in recanalization in all of the patients in this case series without any major side effects. This case series adds to the emerging studies demonstrating the utility of apixaban for CVT.

Keywords

cerebral venous thrombosis, apixaban, unfractionated heparin, direct oral anticoagulation

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Introduction

Cerebral venous thrombosis (CVT) is an uncommon but life-threatening neurological condition that disproportionally afflicts younger patients and females.[1] Prompt recognition and treatment are key to improving the outcome. The standard of care is treatment with anticoagulation to prevent the propagation of the thrombus even in the presence of intracerebral hemorrhage. However, the type of anticoagulation and the duration of treatment are controversial. Patients with CVT have traditionally been treated with unfractionated heparin (UFH) infusion or low molecular weight heparin (LMWH) as a bridge to anticoagulation with vitamin K antagonist (VKA), since the establishment of UFH efficacy in a randomized clinical trial in 1991.[2] Both the European guidelines and American Heart Association (AHA)/ American Stroke Association (ASA) guidelines recommend VKA as a long-term anticoagulant for CVT.[1,3] Direct oral anticoagulants (DOAC) are recommended as first-line therapy over VKA for the management of venous thromboembolism (VTE) other than CVT.[4] Apixaban, a factor Xa inhibitor, is commonly used in the treatment of VTE. The AMPLIFY trial showed apixaban to be non-inferior to conventional therapy (enoxaparin/warfarin) in VTE treatment (pulmonary embolism

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or deep venous thrombosis), with less frequent major bleeding.[5] There is some evidence for the use DOAC in the treatment of CVT. In a small randomized clinical trial, dabigatran, a direct thrombin inhibitor, was found to be equal to warfarin in efficacy and safety for the treatment of CVT.[6] However, there is a paucity of data for the use of apixaban in this patient population.[7] There are a few observational studies but no randomized clinical trials. We present a case series of patients with CVT who were treated with apixaban for long-term anticoagulation. The aim of this study was to evaluate the efficacy and safety of apixaban, the most common used DOAC for CVT at our institution.

Methods

This case series was designed as a retrospective cohort study. We identified and screened all patients diagnosed with CVT at our institution from November 2018 to December 2020. These patients were screened for inclusion criteria that consisted of the following: Radiologically diagnosed CVT with CT venography and/or MR venography and immediate initial treatment with intravenous (IV) anticoagulation for at least twenty-four hours followed by the transition to oral apixaban for long-term anticoagulation. Additional treatment with mechanical thrombectomy was not an exclusion criteria. A total of eleven patients with CVT were identified. Of these, one patient was excluded due to the transition from rivaroxaban to apixaban for recurrent CVT without IV anticoagulation treatment as a bridge. Another patient was excluded due to the transition from IV anticoagulation to dabigatran for long-term anticoagulation. The data for these nine patients were collected by chart review, and include the following: demographics, clinical presentation, radiographical findings, initial treatment, dosing of apixaban, reported adverse events, recanalization rate, time to recanalization, and duration of follow-up.

Results

Patient characteristics are provided in Table 1. Of the nine patients included, five were female (56%). The mean age was 36 years (ranging from 24 to 60). Four patients (44%) had risk factors for CVT (ulcerative colitis, oral contraceptive pill use, anti-thrombin III deficiency, obesity). None of the patients had a history of or active infection with COVID-19. All the patients presented with typical symptoms of CVT. Seven patients (78%) presented with headache, three patients (33%) presented with new onset seizures, and five patients (56%) had additional focal deficits. The diagnosis was confirmed with CT venogram and/or MR venogram. Additional radiological findings were identified and are summarized in Table 2. Radiographic complications of CVT were seen in 56% of patients. These complications include intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and venous infarcts. Two patients (22%) had both IPH and SAH, one patient (11%) had only IPH, and another patient (11%) had only SAH. There were three patients (33%) who had venous infarcts.

Immediately after confirmed diagnosis, all the patients were initially anticoagulated with UFH infusion for at least twenty-four hours, except for one patient (patient number 4), who had anti-thrombin III deficiency and was treated with argatroban infusion, a direct thrombin inhibitor. Eight patients were eventually transitioned to apixaban prior to discharge. One patient (patient number 6) was initially transitioned to dabigatran but was later switched to apixaban after five days due to health insurance coverage. Five patients (56%) received apixaban 10 mg twice daily for the initial five to seven days followed by 5 mg twice daily, based on the stroke neurologist's preference. The remaining four patients (44%) were transitioned from IV anticoagulation to Apixaban 5 mg twice daily. Anticoagulation treatment details are provided in Table 3. Interestingly, there was no worsening of intracerebral hemorrhage and no hemorrhagic conversion of ischemic strokes in any of the patients after the initiation of apixaban, even with the use of a higher dose of apixaban ie, 10 mg twice daily for the first five to seven days.

Follow-up time ranged from six to twenty-three months. There was no progression of the CVT in any of the patients treated with apixaban. There was only one patient who developed anemia after seven months of treatment and required blood transfusion (patient number 6). This patient had a history of uterine fibroids. She was subsequently switched to aspirin as there was already recanalization on the follow-up imaging. None of the other patients reported any adverse

Table 1. Patient Demographics, Comorbidities, and Clinical Presentation.

Patient	Sex	Age	Comorbidities	Clinical presentation
1	F	35	None	Headache, photophobia, nausea, vomiting
2	F	46	Diabetes, hyperlipidemia	Headache, blurry vision
3	M	42	Ulcerative colitis	Headache, right hemiparesis
4	F	60	Depression, anti-thrombin III deficiency	New onset seizure (GTC)
5	M	24	Migraine	New onset seizure (GTC)
6	F	36	Uterine fibroids	Headache, left-sided hearing loss
7	F	25	Migraine without aura, on OCP, obesity, family history of lupus	Headache, left upper extremity paresthesia, new onset seizure (focal onset with secondary generalization)
8	M	26	Recent osteomyelitis, obesity	Headache, intermittent diplopia, intermittent dysarthria, aphasia, papilledema
9	M	36	None	Headache, intermittent diplopia, intermittent facial droop

Abbreviations: F, Female; M, Male; GTC, Generalized tonic clonic; OCP, Oral contraceptive pills.

effects of apixaban. There were no patients who experienced life-threatening hemorrhage or recurrent VTE. Complete recanalization was achieved in seven patients (78%) while two patients (22%) had partial recanalization and were still on apixaban twenty-three months and eight months after the initiation of treatment, respectively. The outcomes and adverse events are summarized in Table 4. Time to complete recanalization varied from four to sixteen months. However, many

Table 2. Radiological Findings.

Patient	CVT location	CVT radiological complications	Other radiological findings
1	Superior sagittal sinus, left transverse sinus, left sigmoid sinus, and proximal right internal jugular vein	None	
2	Left transverse and sigmoid sinuses	IPH right temporal lobe (1.7 × 1.4 cm); SAH	
3	Superior sagittal and left transverse sinuses	Left frontal IPH; SAH	
4	Superior sagittal sinus	SAH parafalcine and left frontal; left frontal lobe infarct	
5	Superior sagittal and bilateral transverse sinuses	None	
6	Left transverse and sigmoid sinuses	Left cerebellar IPH; left temporal lobe infarct	
7	Superior sagittal sinus	Left frontal lobe infarct	
8	Superior sagittal and bilateral transverse sinuses	None	
9	Right transverse sinus, sigmoid, and proximal jugular vein	None	Right mastoid fluid

Abbreviations: IPH, Intraparenchymal hemorrhage; SAH, Subarachnoid hemorrhage.

Table 3. Anticoagulation Treatment.

Patient	IV anticoagulation	Oral anticoagulation	Other treatment
1	IV UFH	Apixaban 5 mg BID	
2	IV UFH	Apixaban 10 mg BID for five days, followed by 5 mg BID	
3	IV UFH	Apixaban 5 mg BID	Mechanical thrombectomy
4	IV Argatroban	Apixaban 10 mg BID for seven days, followed by 5 mg BID	
5	IV UFH	Apixaban 10 mg BID for five days, followed by 5 mg BID	
6	IV UFH	Dabigatran for five days, then switched to Apixaban 5 mg BID	
7	IV UFH	Apixaban 5 mg BID	
8	IV UFH	Apixaban 10 mg BID for seven days, followed by 5 mg BID	Mechanical thrombectomy
9	IV UFH	Apixaban 10 mg BID for seven days, followed by 5 mg BID	

Abbreviations: IV, Intravenous; UFH, Unfractionated Heparin; BID, Twice daily.

Table 4. Outcome and Adverse Effects.

Patient	Worsening of intracranial hemorrhage	Progression of CVT	Adverse effects	Life-threatening bleed	Recurrent VTE	Recanalization	Time to complete or partial recanalization (months)	Follow up duration (months)
1	N/a	No	None	No	No	Yes	14	18
2	No	No	None	No	No	Yes	6	9
3	No	No	None	No	No	Yes	10	11
4	No	No	None	No	No	Yes	6	6
5	N/a	No	None	No	No	Partial	23	23
6	No	No	Anemia[a]	No	No	Yes	7.5	9
7	N/a	No	None	No	No	Yes	16	17
8	N/a	No	None	No	No	Yes[b]	4	6
9	N/a	No	None	No	No	Partial	8	8

Abbreviation: N/a, Not applicable.
[a]Anemia after 6 months on treatment, required 2 units of packed red blood cells.
[b]Recanalized with underlying non-occlusive thrombus.

patients followed up only after several reminders from the clinic, leading to a delay in the initial follow-up imaging.

Discussion

CVT is an uncommon but life-threatening condition with improved outcomes and decreased mortality if correctly diagnosed and promptly treated with anticoagulation. There is limited evidence of the efficacy of DOAC in CVT and variations exist in the clinical practice because there are no large studies or randomized trials evaluating the dosage and duration with the outcomes. The AMPLIFY trial compared apixaban 10 mg twice daily for one week followed by 5 mg twice daily to enoxaparin and warfarin for the treatment of VTE (pulmonary embolism or deep venous thrombosis) and found similar efficacy with less frequent major bleeding in apixaban group.[5] To evaluate long term anticoagulation, AMPLIFY-EXT trial compared apixaban 5 mg twice daily with apixaban 2.5 mg twice daily for VTE treatment (pulmonary embolism or deep venous thrombosis) after six to twelve months of anticoagulation and found no difference.[8] However, there is no comparable trial evaluating safety and efficacy of these two doses in CVT after six to twelve months of treatment.

This case series of patients with cerebral venous thrombosis treated with apixaban demonstrated lack of recurrent thromboembolic events and no major bleeding complications. Apixaban was safe in the treatment of cerebral venous thrombosis, even in the presence of SAH and/or IPH, despite treatment with a higher dose of apixaban, ie, 10 mg twice daily for the first five to seven days in 56% of patients. Anticoagulation with apixaban in CVT prevented recurrent thromboembolic events without life-threatening bleeding complications and promoted cerebral venous recanalization in all of the patients in this case series.

Many authors have reported small case series with three to eight CVT patients treated with apixaban.[9–12] Covut et al reported incomplete recanalization in their case series of five patients after the treatment with apixaban.[9] In this series, two patients (40%) achieved partial recanalization and three patients (60%) achieved no recanalization after 1–18 months follow-up.[9] Another case series by Rao et al reported complete resolution in one patient and partial resolution in two patients.[10] Rusin et al included eight patients in their case series and reported complete recanalization in 50% after three to six months of treatment.[12] Recently, a large retrospective observational study compared DOAC (271 patients on apixaban) with warfarin and found a similar rate of recurrent VTE, death, and recanalization but a lower risk of major hemorrhage.[13] The rate of partial or complete recanalization was reported to be 86% in patients on DOAC without specifying the recanalization rate for apixaban with a median follow-up of 345 days. Our case series is unique with 100% recanalization rate (78% complete recanalization and 22% partial recanalization). Complete recanalization was achieved within four to sixteen months (n: 7). The time to complete recanalization might have been shorter than reported here, as several patients had delayed imaging due to missed follow-up appointments. However, the relatively high rate of recanalization in this case series may be attributed to a longer follow-up time overall.

Conclusion

Our single-center case series is limited by its retrospective nature, small sample size, and lack of systematic follow up. It is difficult to draw any conclusions due to these limitations and a heterogeneous group. This case series adds to the emerging studies demonstrating the utility of apixaban for CVT. Larger randomized clinical trials are warranted to further evaluate the safety and efficacy of apixaban in the treatment of cerebral venous thrombosis.

Declaration of Conflicting Interests

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