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Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience

DOACs in treatment of cerebral venous sinus thrombosis: case series

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ABSTRACT

Aim of the study. Oral anticoagulants, preferentially vitamin K antagonists (VKA), are recommended for 3–12 months in patients with cerebral venous sinus thrombosis (CVST). We present a series of patients with CVST treated with direct oral anticoagulants (DOAC).

Materials and methods. We prospectively recruited 36 patients with CVST (aged 40.3 ± 9.2 years, 58.3% female) treated with DOAC based on the physician's or patient's preferences. Functional outcome was assessed with modified Rankin Scale. Recanalisation was assessed on imaging at 3–6 months post the event. Patients were followed for a median of 30 [interquartile range (IQR) 25–37] months.

Results. After use of heparin (median: 6 days; IQR 5–8.75), patients received dabigatran (150 mg bid, n = 16 or 110 mg bid, n = 2), rivaroxaban (20 mg qd, n = 10) or apixaban (5 mg bid, n = 8) for a median of 8.5 months (IQR 6.25–12). Complete or partial recanalisation was observed in 34 cases (94.4%). Three patients (8.3%) experienced major bleeding: menorrhagia on rivaroxaban (n = 2) and gastrointestinal bleeding on dabigatran (n = 1). A favourable functional outcome was observed in 24 (66.7%) patients, without any fatality. CSVT recurred in two patients (5.6%) and two venous thromboses developed in two other patients with inherited thrombophilia after anticoagulation withdrawal.

Conclusions and clinical implications. DOACs could be an alternative to VKA in CVST patients.

Key words: anticoagulation, cerebral venous sinus thrombosis, direct oral anticoagulants, bleeding, venous thromboembolism

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Introduction

Cerebral venous sinus thrombosis (CVST) is rare, with an annual incidence estimated at 3 to 4 cases per million [1] and with a female to male ratio of 3:1 [2]. CVST is associated with genetic or acquired thrombophilias, malignancy, infection or head trauma, pregnancy, and oral contraceptives [3]. Prothrombotic risk factors are identifiable among 85% of CVST patients [3].

European Stroke Organisation guidelines recommend using low-molecular-weight heparin (LMWH) in the treatment of the acute phase [4], followed by vitamin K antagonists (VKAs) for 3–12 months. The guidelines of the American Heart Association/American Stroke Association are similar [5].

Direct oral anticoagulants (DOACs) are at least as effective as VKAs in the treatment and prevention of the recurrence of venous thromboembolism (VTE) [6]. DOACs might be a promising alternative to VKAs in the long-term treatment of

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CVST, especially among patients for whom VKAs are contraindicated or unsuitable [7].There have been few observational studies on DOAC in CVST. Mendonça et al. [8] reported full recanalisation in 27% of 15 dabigatran-treated CVST patients (mostly 150 mg bid) and excellent long-term functional outcomes in 87% of patients, without any CVST recurrence or major bleeding during follow-ups for a median of 19 months. Geisbüsch et al. [9] reported on seven patients with CVST on rivaroxaban 20 mg qd. During follow-up (median: 7 months), no thrombotic events and two minor bleeds occurred. Complete recanalisation was observed in four patients.

Several experts have advised using DOAC in this disease [6]. To the best of our knowledge, there have been no reports on Polish patients with CVST treated with DOACs. This single-centre case series study was aimed to assess the efficacy and safety of DOACs in CVST.

Materials and methods

We enrolled 36 consecutive patients with a documented episode of CVST referred for further diagnostic work-up to an outpatient clinic at John Paul II Hospital in Krakow, Poland, between December 2013 and March 2018. On the first visit, all eligible subjects were on dabigatran, rivaroxaban or apixaban and provided medical records including imaging data. They were enrolled 3–6 months since a diagnosis of CVST. The exclusion criteria were as follows: indications for long-term anticoagulant therapy other than VTE, diagnosed malignancy, pregnancy, breastfeeding, and advanced kidney disease (stage 4–5). Written consent was obtained to participate in this observational study.

Clinical diagnosis of CVST was made according to the international criteria [5] by brain imaging — computed tomography (CT) with CT venography. Following the use of LMWH at therapeutic doses or unfractionated heparin, the DOAC therapy was initiated. To assess the vessel recanalisation status, CT angiography was performed 3–6 months after CVST.

We collected demographic characteristics, clinical data on CVST, VTE risk factors, comorbidities and current treatment using a standardised questionnaire. Unprovoked CVST was established if there was no history of malignancy, major surgery, trauma, immobilisation, pregnancy or childbirth at least three months before CVST diagnosis and no use of oestrogen. Family history of VTE was defined as VTE in first-degree relatives. Obesity was recognised when Body Mass Index was ≥ 30 kg/m^2.

Follow-up included the time of DOAC use and the time since its withdrawal. Clinical data was collected every six months via a visit to the outpatient clinic or telephone contact. The decision to cease DOAC use was left to the discretion of the attending physician based on the patient's preferences. Thrombophilia screening was performed (antiphospholipid syndrome [APS], Factor V Leiden [FVL] or prothrombin G20210A mutations and deficiencies in protein C, protein S or antithrombin, as described previously [10]). Functional outcome was assessed using modified Rankin Scale (mRS) before initiation of the DOAC therapy and after 6–12 months of follow-up. A favourable functional outcome was defined as 0-1 point in mRS. The occurrence of VTE (including CVST) and major bleeding (according to the definition by Schulman et al. [11]) were recorded.

The local ethical committee issued approval for the study according to the Declaration of Helsinki.

Statistical analysis

Categorical variables were reported as numbers and percentages. Continuous variables were presented as means (standard deviation) or median (IQR, interquartile range). Normality was assessed by the Shapiro-Wilk test. The chi-squared test was used to compare categorical variables. The ANOVA or Kruskal-Wallis tests for continuous variables were conducted to assess differences between the groups using different DOACs. Analyses were performed using SPSS Software (IBM, USA). A P-value below 0.05 was considered statistically significant.

Results

A total of 36 patients with CVST (aged 40.3 ± 9.2 years, 58.3% female) were analysed (Table 1). Unprovoked CVST was found in 26 (72.2%). Thrombophilia was observed in 18 (50%) patients, including eight patients (22.2%) with FVL.

The most common single location of CVST was the transverse sinus. Following the use of heparin (median, 6 days; IQR 5–8.75), DOAC was initiated and continued for a median of 8.5 months (IQR 6.25–12). There were 18 patients (50%) on dabigatran (n = 16, 150 mg bid and n = 2, 110 mg bid). Ten subjects (27.8%) received rivaroxaban (20 mg daily) and eight patients (22.2%) were on apixaban (5 mg bid). Apart from older age in the dabigatran users (44.3 ± 8.3 years *vs.* rivaroxaban 35.7 ± 9.1 and apixaban 37.1 ± 8.4 years, p = 0.029), the patients on the three DOACs were similar with regard to demographic and clinical characteristics (data not shown).

A repeat brain imaging after 3–6 months showed at least partial vessel recanalisation in 34 patients (94.4%). Complete recanalisation was observed in 20 individuals (55.6%), comprising 10 on dabigatran (55.6%), six on rivaroxaban (60.0%) and four on apixaban (50.0%).

On anticoagulant therapy, three patients (8.3%), two on rivaroxaban (20 mg qd) and one on dabigatran (110 mg bid), experienced major bleeding, including two heavy menstrual bleedings (HMB) in a 25-year-old woman and a 46-year-old woman both with previously abundant menses (haemoglobin, 8 g/dL and 9 g/dL, respectively) and an upper gastrointestinal bleeding in a 56-year-old woman who had reported dysphagia in previous weeks despite pantoprazole use.

Table 1. Characteristics of the study participants

VARIABLE	TOTAL (n = 36)
Age, years	40.3 ± 9.2
Sex female, n (%)	21 (58.3%)
BMI [kg/m^2]	26.8 ± 4.2
Cigarette smoking, n (%)	8 (22.2%)
OC/HRT, n/females (%)	10/21 (47.6%)
Family history of VTE, n (%)	8 (22.2%)
Unprovoked CVST, n (%)	26 (72.2%)
Obesity, n (%)	10 (27.8%)
Site of CVST	
Transverse sinus, n (%)	5 (13.9%)
Cavernous sinus, n (%)	3 (8.3%)
Straight sinus, n (%)	1 (2.8%)
Combined, n (%)	26 (72.2%)
Other locations, n (%)	1 (2.8%)
Concomitant VTE, n (%)	4 (11.1%)
Heparin regimen	
LMWH, n (%)	33 (91.7%)
UFH, n (%)	3 (8.3%)
Duration of heparin use [days]	6 (5–8.75)
Aspirin use, n (%)	8 (22.2%)
Type of DOAC	
Dabigatran, n (%)	18 (50.0%)
Rivaroxaban, n (%)	10 (27.8%)
Apixaban, n (%)	8 (22.2%)
Full dose of DOAC, n (%)	34 (94.4%)
Duration of DOAC use [months]	8.5 (6.25–12)
mRS score at the start of DOAC	
Favourable outcome (mRS 0–1), n (%)	19 (52.8%)
Independent (mRS 2), n (%)	13 (36.1%)
Significant disability (mRS 3–5), n (%)	4 (11.1%)
Follow-up [months]	30 (25–37)
Recanalisation 3-6 months after CVST	
Complete, n (%)	20 (55.6%)
Partial, n (%)	14 (38.9%)
No recanalisation, n (%)	2 (5.6%)
mRS score 6-12 months after CVST	
Favourable outcome (mRS 0–1), n (%)	24 (66.7%)
Independent (mRS 2), n (%)	10 (27.8%)
Significant disability (mRS 3–5) , n (%)	2 (5.6%)
Recurrent CSVT, n (%)	2 (5.6%)
New DVT, n (%)	2 (5.6%)
Major bleeding, n (%)	3 (8.3%)
Thrombophilia testing	
Factor V Leiden, n (%)	8 (22.2%)
Prothrombin G20210A mutation, n (%)	3 (8.3%)
Protein C deficiency, n (%)	1 (2.8%)
Protein S deficiency, n (%)	2 (5.6%)
Antithrombin deficiency, n (%)	1 (2.8%)
Antiphospholipid syndrome, n (%)	4 (11.1%)

Data reported as median (interquartile range), mean ± standard deviation or number (percentage)
BMI — Body Mass Index; CVST — cerebral venous sinus thrombosis; DVT — deep vein thrombosis; LMWH — low-molecular-weight heparin; mRS — modified Rankin Scale; DOAC — direct oral anticoagulant; OC/HRT — oral contraceptives/hormonal replacement therapy; UFH — unfractionated heparin; VTE — venous thromboembolism

After withdrawal of anticoagulant therapy, we followed patients for a median of 30 months (IQR 25–37). Neurological evaluation at 6–12 months showed that 66.7% of CVST patients (n = 24) had a favourable functional outcome. During follow-up, two patients (5.6%) had recurrent CVST. One episode occurred in a 37-year-old man, free of thrombophilia but with a positive VTE family history, five months after rivaroxaban withdrawal. The other was diagnosed in a 52-year-old woman, diagnosed with single-positive APS, following hospitalisation for pneumonia, 20 months after the first CSVT, while on aspirin. There were also two episodes of deep-vein thrombosis (DVT). The first DVT event, provoked by a leg injury and oral contraception, occurred in a 29-year-old woman heterozygous for prothrombin G20210A mutation with previous VTE, 18 months after apixaban therapy was ended. The other unprovoked DVT was observed in a 46-year-old woman heterozygous for FVL.

Discussion

To the best of our knowledge, this is the first Polish case study and the largest worldwide report presenting treatment outcomes among DOAC-treated patients with CVST.

We noted complete cerebral vessel recanalisation in more than 55% of rivaroxaban users, which is similar to the previous study [9], in which such an outcome was observed in 57.1% of cases. Among dabigatran-treated patients, the complete recanalisation rate was 60% (n = 6), which is much higher than in a Portuguese study [8] where full recanalisation was noted in 26.7% of patients. The favourable functional outcomes during follow-up were similar to previous studies [8–9] while a favourable functional outcome was observed in 58–89% of CVST patients on warfarin [12–13].

Since among VKA-treated patients with CVST, the major bleeding rate is estimated at 0.21%/patient-month [14], the present rate with 8.3% of patients (n = 3) with major bleeding over a median of 8.5 months of DOAC therapy appears to be higher. However, there were no life-threatening episodes and the 50% lower risk of intracranial bleeds on DOAC is of vital importance. We confirmed an increased HMB risk on this drug [15–16], which supports the suggestion that in women of reproductive age and previously abundant menses, rivaroxaban should be avoided. Previous small studies [8–9] did not report any major haemorrhages, which disagrees with randomised VTE studies and registries [17–18].

Two recurrent episodes of CVST while off anticoagulation are consistent with the rates reported in previous studies, i.e. 2–4.4% over a median 16–40 months of follow-up (0.5–1.5 per 100 person-years) [3, 12]. Regarding non-cerebral VTE, the current two episodes among 36 CVST patients correspond to the rate for VKA-treated CVST patients (6.5% over a median follow-up of 40 months) [12].

Clinical implications/future directions

While we await the results of a randomised trial with dabigatran in CVST patients [19], based on growing evidence from observational studies, DOACs do appear to be an attractive alternative to VKA due to similar efficacy and safety without even taking into account advantages including no need for laboratory monitoring, no dietary interactions, and no interference with most medications [20]. Randomised trials with all DOACs should be performed to prove the benefits available from DOACs in this disease.

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