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Direct oral anticoagulants versus warfarin in the treatment of cerebral venous thrombosis in Bach Mai hospital

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ABSTRACT

Cerebral venous thrombosis (CVT) is a rare type of stroke that carries a risk of recurrence, including conditions such as limb venous thrombosis and pulmonary thrombosis… A cross-sectional study conducted at Bach Mai Hospital from January 2022 to June 2024 evaluated the safety and efficacy of oral anticoagulants, including direct oral anticoagulants (DOAC) and warfarin, in 47 patients diagnosed with cerebral venous thrombosis. The study found that the average age of the participants was 44.7 ± 16.8 years. The complete recanalization rates for the groups using DOAC and warfarin were 80.5% and 66.7%, respectively. Additionally, the proportion of patients achieving a favorable recovery, indicated by an mRS score of 0-1, was 80.5% for the DOAC group and 83.3% for the warfarin group. Importantly, the rates of recurrent venous thrombosis and bleeding events were low, at 2.4% and 4.9%, respectively. This study provides valuable information regarding the efficacy and safety of both DOAC and warfarin for patients with CVT, aiding clinicians in making informed decisions about anticoagulant therapy.

Keywords: cerebral venous thrombosis, anticoagulants, DOAC, warfarin.

I. INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare type of stroke, representing 0.5-3% of all hospitalized stroke cases. It has an incidence rate of 5 per million people each year and most commonly affects young individuals.[1,2] Patients who have experienced the acute phase of CVT are at a high risk of recurrent venous thromboembolism (VTE) in the cerebral venous sinuses, lower limb veins, and pulmonary veins.[3] Most relapses happen within the first few months of the illness.

Early diagnosis and anticoagulant treatment of CVT significantly improve treatment effectiveness. Initiating anticoagulant therapy early in CVT can reverse the pathological process, reduce complications during the acute phase, and lessen the disease's long-term effects[4]. The recommended treatment for preventing the recurrence of VTE after CVT includes the use of vitamin K antagonists (VKAs) or direct oral anticoagulants (DOAC). The duration of treatment typically ranges from 3 to 12 months, but it may be extended beyond this period based on the individual risk factors of each patient.[1,5]

Warfarin is a commonly used, low-cost medication that has been shown to be highly effective in treating and preventing venous thrombosis when the anticoagulant effect is maintained within an INR of 2-3. However, it has a narrow therapeutic range, making it essential to find a stable dosage to ensure safety and treatment effectiveness while minimizing complications. This requirement complicates the monitoring of the treatment process. The direct oral anticoagulants (DOACs) have been officially included in the 2024 treatment recommendations for CVT by the American Heart Association (AHA). However, there have been few comparative studies assessing the effectiveness and safety of DOAC versus warfarin. To address this gap, we conducted a study with the objective of describing the safety and effectiveness of warfarin and DOAC in patients diagnosed with CVT in Bach Mai Hospital.

II. SUBJECT AND METHOD

1. Subject

Inclusion criteria: This diagnosis pertains to patients at Bach Mai Hospital from January 2022 to June 2024. To be considered a gold standard for CVT diagnosis on brain MRI images, patients must meet all of the following criteria:

Conventional Pulse Sequences (T1W, T2W, FLAIR): There should be a loss of the empty flow signal in the cerebral venous sinus or cerebral vein, which is then replaced by the signal of the thrombus in various stages.

2D Time-of-Flight (TOF) Image: There should be no flow signal present in the cerebral venous sinus or cerebral vein.

3D T1 Image after Contrast Administration: There should be no complete or partial enhancement within the sinus or vein, but the formation of the sinus should still be visible.

Additional criteria include:

Age: Patients must be at least 18 years old.

Clinical Condition: Patients should be clinically stable after undergoing standard low molecular weight heparin treatment for a duration of 5 to 15 days.

Exclusion criteria:

- CVT associated with central nervous system infection, head trauma.

- Patients planning surgery to treat CVT (eg: intracranial decompression surgery, ENT surgery...).

- Conditions associated with a high risk of bleeding, including:

+ History of gastrointestinal bleeding in the last 6 months.

+ Planned surgery in the next 6 months.

+ Coagulation disorders.

+ Platelets < 100 G/L.

+ Uncontrolled hypertension > 180/100mmHg.

- Life-threatening bleeding or major bleeding other than intracranial bleeding during CVT treatment.

- Postpartum within 6 weeks, pregnancy, planning pregnancy within 1 year.

- Patients who do not comply with treatment or do not return for a check-up after treatment.

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- The patient or the patient's family refuses to participate in the research.

2. Method

This study is a cross-sectional descriptive analysis that included a sample of 47 patients. Data were collected, entered, and analyzed using SPSS version 20.0 statistical software. A significance level of $p < 0.05$ was used for determining statistical significance. For qualitative variables, descriptive parameters included frequency and percentage values, and proportions between qualitative variables were compared using the Chi-square test. For quantitative variables, we reported the mean, standard deviation, and median. To compare mean values between two groups, the student t-test was utilized, while for three or more groups, the ANOVA test was employed. Hypothesis testing for independent variables was conducted using the Mann-Whitney U test for two groups and the Kruskal-Wallis test for three or more groups.

III. RESULT

***Table 1**. Distribution of patients based on age groups.*

Age/ Gender		Male n=21 (44,7%)	Female n=26 (53,3%)	General n=47 (100%)
Age (mean ± SD) (Age range)		46.8 ± 14.5 (20 – 68 tuổi)	43.0 ± 18.5 (17 – 90 tuổi)	44.7 ± 16.8 (17 – 90 tuổi)
Distribution by age group	18 - ≤ 20	1 (2.1%)	2 (4.3%)	3 (6.4%)
	21 - 30	3 (6.4%)	4 (8.5%)	7 (14.9%)
	31 - 40	4 (8.5%)	9 (19.1%)	13 (27.6%)
	41 - 50	4 (8.5%)	5 (10.6%)	9 (19.1%)
	51 - 60	4 (8.5%)	2 (4.3%)	6 (12.8%)
	61 - 70	5 (10.6%)	2 (4.3%)	7 (14.9%)
	≥ 71	0 (0%)	2 (4.3%)	2 (4.3%)

The study involved 47 patients, with an average age of 44.7 years (± 16.8). The youngest participant was 17 years old, while the oldest was 90. The average age of male patients was 46.8 years (± 14.5), and the average age of female patients was 43.0 years (± 18.5). The most represented age group was between 21 and 50 years old, comprising 61.7% of the participants.

***Table 2**. Duration of hospital stay in days.*

Duration of hospital stay in days	DOAC only (n =41)	Warfarin only (n=6)	General
Mean ± SD	13.1 ± 5,2	16.7 ± 3,3	13.5 ± 5,2
Min	6	14	6
Max	32	23	32

Out of 47 patients, 41 were treated with DOAC while 6 were on warfarin following Lovenox treatment. The average hospital stay for the study group was 13.5 days, with a standard deviation of 5.2 days. The shortest hospital stay was 6 days and the longest was 32 days. In the DOAC group, the average hospital stay was 13.1 days (± 5.2 days), whereas in the warfarin group, it was 16.7 days (± 3.3 days).

***Table 3**. atient's condition at discharge and after 12 weeks.*

Modified Ranking Score (mRS)	DOAC only (n =41)		Warfarin only (n=6)	
	Discharge	After 12 weeks	Discharge	After 12 weeks
0-1	29 (70.7%)	33 (80.5%)	5 (83.3%)	5 (83.3%)
2	3 (7.3%)	4 (9.8%)	0 (0%)	0 (0%)
3	4 (9.8%)	4 (9.8%)	0 (0%)	1 (16.7%)
>3	5 (12.2%)	0 (0%)	1 (16.7%)	0 (0%)
Sum	41		6	
Mean ± SD	1.12 ± 1.45	0.59 ± 1.02	0.83 ± 1.60	0.50 ± 1.23

After 12 weeks of treatment, the rate of patients with good recovery, achieving an ideal mRS score of 0-1 points, was high in both groups, at 80.5% and 83.3%, respectively. No patient in either group experienced severe functional loss, with mRS>3.

***Table 4**. Recanalization of the venous sinus after a duration of 12 weeks.*

Recanalization Grade	DOAC only (n =41)		Warfarin only (n=6)	
	n	%	n	%
Complete recanalization	33	80.5	4	66.7
Partial recanalization	8	19.5	2	33.3
Non-recanalization	0	0	0	0
Sum	41	100	6	100

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At 12 weeks of treatment, the rates of complete recanalization were 80.5% in the DOAC group and 66.7% in the warfarin group. The remaining patients experienced partial recanalization.

***Table 5**. Venous thromboembolic events occurring within 12 weeks*

Event	DOAC only (n =41)		Warfarin only (n=6)	
	n	%	n	%
Recurrent CVT	0	0	0	0
Limb Venous Thrombosis	1	2.4	0	0
Visceral venous thrombosis	0	0	0	0
Pulmonary Embolism	0	0	0	0

Over 12 weeks of follow-up, there was one case of recurrent lower limb venous thrombosis in patients using DOAC, representing 2.4%. Additionally, no cases of recurrent CVT, visceral venous thrombosis, or pulmonary embolism were reported in either group.

***Table 6**. Bleeding events within 12 weeks*

Event	DOAC only (n =41)		Warfarin only (n=6)	
	n	%	n	%
Intracranial bleeding	2	4.9	0	0
Gastrointestinal bleeding	0	0	0	0
Menorrhagia	0	0	0	0
Other bleeding	0	0	0	0

During a 12-week follow-up, two patients in the DOAC group experienced cerebral hemorrhage, representing 4.9% of the cases.

DISCUSSION

Our study involved 47 patients diagnosed with CVT who were treated during the acute phase with low molecular weight heparin (LMWH) for a duration of 5 to 15 days. Following this initial treatment, patients continued on either DOAC or warfarin, and they were monitored and evaluated after 12 weeks of treatment. The results indicated that the mean age of the study group was 44.7 ± 16.8 years, with ages ranging from 17 to 90 years. Notably, women experienced a younger age of onset compared to men, with a mean age of 43.0 ± 18.5 years for females and 46.8 ± 14.5 years for males. The most common age group among the patients was 21 to 50 years old, accounting for 61.7% of cases. For comparison, the mean age of onset in the RE-SPECT CVT and ACTION-CVT studies was reported as 45.2 years and 44.8 years, respectively.[6,7]

In our study, the average duration of

treatment in the study group was 13.5 ± 5.2 days. The treatment duration varied based on the clinical severity of the condition, with a minimum of 6 days and a maximum of 32 days. For patients treated with DOAC, the average treatment duration was 13.1 ± 5.2 days, while for those treated with warfarin, it was 16.7 ± 3.3 days. In the ISCVT study conducted by Ferro et al, the average hospital stay was reported to be 20.4 ± 14.3 days. Similarly, Khealarri et al in a study of patients with CVT in the Middle East, found an average hospital stay of 9 days.[8] The differences in hospital stay observed between these studies can be attributed to the variability in brain parenchymal lesions and the clinical severity of CVT, as well as the differences in diagnostic and treatment facilities across different countries. Notably, the length of hospitalization for patients on warfarin was longer than for those using DOACs. This is because transitioning from injectable anticoagulants to oral ones requires additional time to adjust the warfarin dosage in order to reach the optimal INR range of 2-3. In contrast, newer generation anticoagulants such as DOACs do not necessitate dose adjustments.

In a study involving 47 patients, 41 were treated with DOAC while the remaining 6 were on warfarin following treatment with low molecular weight heparin. The discharge rates for patients achieving complete recovery, indicated by a modified Rankin Scale (mRS) score of 0-1, were 70.7% in the DOAC group and 83.3% in the warfarin group. After 12 weeks of treatment, both groups showed high rates of good recovery, with mRS scores of 0-1 at 80.5% for the DOAC group and 83.3% for the warfarin group. In comparison, the ISCVT study indicated that at discharge, the overall rate of complete recovery (mRS score of 0-1) was 65.7%, which increased to 78.1% six months after treatment.[3] In comparison, the ISCVT study indicated that at discharge, the overall rate of complete recovery (mRS score of 0-1) was 65.7%, which increased to 78.1% six months after treatment.[6] Meanwhile, the RESPECT-CVT study reported that at discharge, the recovery rates in the Dabigatran group and the Warfarin group were 91.1% and 89.7%, respectively. At 24 weeks, these rates remained high at 91.5% for the Dabigatran group and 91.4% for the warfarin group.[9] The results of our study, along with those from both domestic and international authors, indicate a very positive outcome for patients with CVT experiencing almost complete recovery, as measured by a mRS score of 0-1. The recovery rate at the time of discharge ranged from 60% to 91.1%, and after three months of treatment, it improved to approximately 80% to 94.7%. These encouraging results are likely due to the close collaboration between treating physicians and the diagnostic imaging department. The advancements in modern diagnostic imaging methods have facilitated early diagnosis, supported by updated recommendations, treatment regimens, and management strategies for CVT.

At 12 weeks of treatment, the complete recanalization rates were 80.5% for patients receiving DOAC and 66.7% for those on warfarin. A study conducted by Maqsood et al, involving 45 patients with CVT in South Asia, reported that at the 12-week mark, the venous sinus recanalization rate in the DOAC group was 71%. Within this group, 57% experienced complete recanalization, while 14% had partial recanalization. In the warfarin group, the overall recanalization rate was also 71%, with complete recanalization at 38% and partial recanalization at 33%. At 12 months of treatment, both groups reached a recanalization rate of 100%, with the complete recanalization rate being 90% for the

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DOAC group and 89% for the warfarin group.[10]

In our study, during a 12-week follow-up period, we observed one case of recurrent lower limb venous thrombosis in patients treated with DOAC, which represents 2.4% of the cases. There were no recorded instances of recurrent CVT, visceral venous thrombosis, or pulmonary embolism in either group. Overall, we found that the rate of VTE events in patients with CVT who received maintenance prophylaxis with either DOAC or warfarin was low, indicating effective treatment in preventing recurrent thrombosis. Additionally, Maqsood's study reported that after a 12-month follow-up, there were no recurrent venous thromboembolic events, including CVT, limb venous thrombosis, pulmonary embolism, or visceral embolism.[10] Similarly, in the RE-SPECT study, after 24 weeks of follow-up, no cases of recurrent venous thromboembolism were recorded in either group of patients receiving DOAC or warfarin.[6]

During the 12-week follow-up period, the rate of bleeding was low among the participants. Of the 47 patients in the DOAC group, 2 experienced cerebral hemorrhage, which represents 4.9% of that group, and no other bleeding events were reported in either group. In a study conducted by Yy in China, after 90 days of treatment, 38 patients treated with DOAC experienced a minor bleeding event rate of 7.9%, which included one case of gastrointestinal bleeding (2.6%). In contrast, among 45 patients treated with warfarin, there were 4 cases of minor bleeding (8.9%), with no cases of major bleeding.[11] The RE-SPECT study reported 3 cases of major bleeding: 1 case of gastrointestinal bleeding in the DOAC group (1.7%) and 2 cases of cerebral bleeding in the warfarin group (3.3%).[6] Overall, all studies indicated that the rate of bleeding events in patients with CVT treated with either DOAC or warfarin was very low. This suggests that the use of anticoagulants is safe for treating CVT. However, some cases of severe bleeding still occurred in both groups, highlighting the importance of regular monitoring and management of patients after they are discharged from the hospital to help minimize potential complications.

CONCLUSION

This study evaluated the safety and efficacy of direct oral anticoagulants and warfarin for patients with cerebral venous thrombosis at Bach Mai Hospital, assisting clinicians in making appropriate treatment decisions for patients with this condition in Vietnam.

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