Current Journal of Neurology

Original Paper

Curr J Neurol 2021; 20(3): ?-?

Evaluation of rivaroxaban versus warfarin for the treatment of cerebral vein thrombosis: The first case-control blinded study

Received: 12 Mar. 2020
Accepted: 10 May 2021

Fariborz Khorvash[1], Mohammad Javad Farajpour-Khanaposhtani[2], Helia Hemasian[2], Sayed Mohammad Saadatnia[1]

[1] Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Keywords
Cerebral Veins; Thrombosis; Warfarin; Rivaroxaban

Abstract

Background: Anticoagulation therapy following cerebral vein thrombosis (CVT) can improve mortality and morbidity. Vitamin K antagonists are currently the routine oral anticoagulant used for CVT; while by introduction of rivaroxaban, a direct factor Xa inhibitor, the attentions have been deviated toward novel agents, but the evidence is not strong. The current study is aimed to compare the efficacy and safety of rivaroxaban versus warfarin for anticoagulation therapy of CVT.

Methods: The current randomized clinical trial has been conducted on 50 patients with CVT among which, 25 ones were randomly allocated to rivaroxaban treatment (20 mg per day for three months) and remained 25 ones to warfarin treatment [adjusted based on international normalized ratio (INR) of 2-3]. The Modified Rankin Scale (mRS) and clinical investigations, including the incidence of seizure, papilledema, intra/extra-cranial bleeding, blurred vision, headache, nausea and vomiting, and death were evaluated at discharge time and within 3 and 6 months following CVT incidence; eventually, two groups were compared.

Results: Comparison of mRS scores between the groups revealed significant differences in none of the interval assessments, at the time of admission ($P = 0.51$), within three months ($P = 0.63$), and within six months ($P = 0.99$), while both of the approaches led to significant decrease in mRS scores following both of the treatments ($P < 0.001$). The comparison of drug-related adverse effects showed insignificant difference between warfarin versus rivaroxaban ($P > 0.05$).

Conclusion: Based on this study, rivaroxaban is an efficacious agent for the treatment of CVT without remarkable adverse effects.

How to cite this article: Khorvash F, Farajpour-Khanaposhtani MJ, Hemasian H, Saadatnia SM. Evaluation of rivaroxaban versus warfarin for the treatment of cerebral vein thrombosis: The first case-control blinded study. Curr J Neurol 2021; 20(3): ?-?.

Corresponding Author: Sayed Mohammad Saadatnia
Email: mosaadatnia@yahoo.com

Introduction

Cerebral vein thrombosis (CVT) is a relatively uncommon type of stroke involving cerebral vein and/or sinuses. This type of stroke accounts for only 0.5%-1.0% of all strokes, while it can cause death in less than 5% or significant complications such as lifelong dependency in 15% of the cases.[1-3] The prevalence of CVT ranges from 1.3 to 1.6 cases per 100000 persons in high-income countries, while it is higher in low- to moderate-income communities.[4-6]

The routine therapeutic approach for CVT is anticoagulant therapy initiated with intravenous (IV) heparin continued by oral agents. Currently, oral anti-vitamin K agent, warfarin, for 3-6 months, is the gold standard one; however, investigations regarding the other anticoagulant agents with appropriate efficacy and better safety are in progress.[7]

Those who survive the acute CVT are at increased risk of developing venous thrombosis events, not only in cerebral veins but in other parts such as pulmonary thromboembolism, the vein of the limbs, and splanchnic veins.[3,8] The risk of recurrence in CVT is higher only within a few months after the acute thrombosis.[9] Therefore, the early initiation of anticoagulant therapy can help appropriate treatment and prevention of thrombosis recurrence.[10-12]

In the recent few years, direct factor Xa inhibitor, rivaroxaban, has been introduced. Investigations in terms of rivaroxaban use as an anticoagulant agent in CVT are already limited, in which rivaroxaban was not inferior to injecting anticoagulant plus oral anti-vitamin K agents.[13] Besides, the incidence of anticoagulant-related intracranial bleeding or fatal bleeding was dramatically less in rivaroxaban-treated cases as compared to the warfarin-treated ones.[1]

Studies regarding the use of rivaroxaban for the treatment of CVT are at early stages and limited to observational ones. Therefore, the current study was aimed to compare the safety and efficacy of rivaroxaban versus warfarin for the treatment of CVT.

Materials and Methods

Study participants: The current randomized clinical trial has been conducted on 50 patients with CVT admitted at Alzahra Hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from April 2018 to May 2019. Those over 18 years old with the diagnosis of CVT confirmed with venography [either through computed tomography (CT) or magnetic resonance imaging (MRI)] were included. Septic or traumatic CVT, impaired renal function [glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2], pregnancy, reluctance for participation in the study, withdrawal from the study, patients with contraindications for oral anticoagulation, and non-adherence to the medical therapy were the exclusion criteria. The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol. Besides, it has been recorded in the registry of ClinicalTrials.gov encoded NCT03747081. After that, the study protocol was explained for the participants or their legal guardians, and written consent for participation in the study was obtained.

The patients who met the inclusion criteria were included in the study through convenience sampling consequently. After that, they were randomly allocated to treatment groups (warfarin or rivaroxaban) using Random Allocation software. Therefore, each of the patients was provided with a particular number that allocated her/him to one of the treatment groups.

In order to minimize the interobserver bias, a skilled neurologist blinded to the type of the treatment approach performed all of the neurological assessments. Besides, the statistician was blinded to the treatments as they were encoded as group A and B.

Treatment protocol

Rivaroxaban: This group was primarily treated with 60 mg of subcutaneous enoxaparin (Caspian Tamin Co., Iran) twice daily for the first two days. Then, as soon as enoxaparin therapy cessation, the rivaroxaban regimen with the protocol of 20 mg per day (Xalerban, Abidi Co., Iran) was initiated for six months.

In cases with a GFR of less than 50 ml/min/1.73 m^2 using Cockcroft measurements, 15 mg of rivaroxaban was prescribed.

Warfarin: The second group was primarily treated with 60 mg of enoxaparin twice daily and in case of capability for oral administration of the drugs, concurrent warfarin therapy was initiated, as well. The bridging therapy with two agents continued until achieving the international normalized ratio (INR) of 2-3; after that, enoxaparin therapy was discontinued, and only treatment with warfarin for six months went on. The dosage of warfarin therapy was determined based on the patient's INR, assessed once a week.

Clinical assessments: The patient's demographics and medical history data including

age, gender, oral contraceptive therapy within the previous month, sinusitis, being in the post-partum phase, history of renal failure, recent medical therapy, pregnancy, and immobility within the previous month were recorded in the study checklist.

The status of renal function was assessed based on the Cockcroft-Gault formula and by measurement of the patients' creatinine in a reference laboratory of Alzahra Hospital. Besides, the recent history of immobility was defined as immobility for over 12 hours in the previous month due to hip fracture, malignancy, paralysis, or other reasons, and also due to air travel.

The primary outcome of this study was neurological assessments using the Modified Rankin Scale (mRS), done by a skilled neurologist, at the time of hospital admission, within three months, and eventually, within six months of follow-up.

Other investigations included the incidence of seizure, papilledema, intra- or extra-cranial bleeding, blurred vision, double vision, headache, nausea and vomiting, and death. These assessments were performed at the time of admission and within three and then, six months following the CVT incidence, to follow the patients regarding their CVT-related clinical view and also treatment adverse effects.

The mRS is a means to assess the disabilities and dependency of the patients with stroke or other neurological diseases in daily activities scored from 0 to 6.[14]

The obtained data were entered into the SPSS software (version 23, IBM Corporation, Armonk, NY, USA). The descriptive data were presented in mean, standard deviation (SD), absolute numbers, and percentages. For analytics, chi-square test, Fisher's exact test, Mann-Whitney test, t-test, and Friedman test were used. P-value of less than 0.05 was considered as a significant level.

Results

In the current study, eligibility of 64 patients for participation in the study was assessed, among which 14 ones were excluded due to renal failure (n = 4), septic or traumatic CVT (n = 6), and pregnancy (n = 4). Among the remained 50 ones, 25 patients were allocated to the warfarin regimen, and the latter 25 ones to rivaroxaban treatment. The mean age of the study population was 41.98 ± 11.42 years (age range of 26-84 years) with a gender distribution of 36 women (72%) and 14 men (28%).

The mean age of the rivaroxaban-treated group was 41.20 ± 11.35 years, among which 17 ones (68%) were women, while the mean age of warfarin-treated patients was 40.76 ± 11.72 years and 19 ones (76%) were women. Table 1 demonstrates the medical and demographic data of the studied groups, in which the two groups were similar in terms of age (P = 0.890), gender distribution (P = 0.520), oral contraceptive pill (OCP) administration (P = 0.500), recent immobility, and hereditary coagulation disorders.

Comparison of mRS scores between the groups revealed insignificant differences between the groups in none of the interval assessments, at the time of admission (P = 0.510), within three months (P = 0.630), and within six months (P = 0.990), while Friedman test showed that both of the approaches led to significant decrease in mRS scores following both of the treatments (P < 0.001) (Table 2).

Furthermore, the comparison of the two groups regarding CVT-related complications and treatment-related complications is demonstrated in table 3.

Table 1. Comparison of demographic and medical data of the two assessed groups

Variables		Rivaroxaban	Warfarin	P
Age (year) (mean ± SD)		41.20 ± 11.35	40.76 ± 11.72	0.890*
Gender [n (%)]				
	Women	17 (68.0)	19 (76.0)	0.520**
	Men	8 (32.0)	6 (24.0)	
Oral contraceptive [n (%)]		5 (20.0)	7 (28.0)	0.500**
Recent immobility [n (%)]		1 (4.0)	1 (4.0)	-
Hereditary coagulation disorders [n (%)]		0 (0)	0 (0)	-
Use of antihypertensive and antidiabetic agents [n (%)]		4 (16.0)	5 (20.0)	0.990£
Type of infarction [n (%)]				
	No infarct	19 (76.0)	15 (60.0)	0.640£
	Hemorrhagic infarction	3 (12.0)	6 (24.0)	
	Non-hemorrhagic infarction	3 (12.0)	4 (16.0)	

*T-test; **Chi-square test; £Fisher's exact test
SD: Standard deviation

Table 2. Comparison of Modified Rankin Scale (mRS) between the studied groups

	Rivaroxaban [median (first quartile, third quartile]	Warfarin [median (first quartile, third quartile)]	P
At admission	3 (1.5, 4.0)	3 (2.0, 4.0)	0.510*
Within three months	1 (0, 1.0)	1 (0, 2.0)	0.630*
Within six months	0 (0, 1.0)	0 (0, 2.0)	0.990*
P	< 0.001**	< 0.001**	

*Mann-Whitney test; **Friedman test

Treatment with both of the agents led to significant reduction in all of the symptoms (P < 0.050), while comparison of rivaroxaban with warfarin revealed insignificant differences (P > 0.050) except for blurred vision that was remarkably higher among rivaroxaban-treated patients within three months (P = 0.034) but in the next assessment of sixth months (P = 0.600). A comparison of the two groups regarding the incidence of intra-cranial or extra-cranial bleeding due to the treatments revealed insignificant differences in both three-month and six-month interval assessments (P > 0.050).

Table 3. Comparison of post-cerebral vein thrombosis (CVT) complications and drug-related adverse effects between the study groups

Variable	Time of assessment	Rivaroxaban [n (%)]	Warfarin [n (%)]	P
Headache (yes/no)	At admission	22 (88.0)/3 (12.0)	23 (92.0)/2 (8.0)	0.990*
	Within three months	11 (44.0)/14 (56.0)	13 (52.0)/12 (48.0)	0.570**
	Within six months	8 (36.4)/14 (63.6)	7 (30.4)/16 (69.6)	0.670**
P		< 0.001	< 0.001	
Blurred vision (yes/no)	At admission	14 (46.0)/11 (44.0)	9 (36.0)/16 (64.0)	0.150**
	Within three months	8 (32.0)/17 (68.0)	2 (8.0)/23 (92.0)	0.034**
	Within six months	2 (9.1)/20 (90.9)	1 (4.3)/22 (95.7)	0.600*
P		0.002	0.001	
Double vision (yes/no)	At admission	6 (24.0)/18 (76.0)	2 (8.0)/23 (92.0)	0.240*
	Within three months	2 (8.0)/23 (92.0)	1 (4.0)/24 (96.0)	0.990*
	Within six months	0 (0)/22 (100)	1 (4.3)/22 (95.7)	0.990*
P		0.010	0.380	
Nausea (yes/no)	At admission	14 (56.0)/11 (44.0)	15 (60.0)/10 (40.0)	0.770**
	Within three months	3 (12.0)/22 (88.0)	2 (8.0)/23 (92.0)	0.990*
	Within six months	0 (0)/22 (100)	1 (4.3)/22 (95.7)	0.990*
P		< 0.001	< 0.001	
Vomiting (yes/no)	At admission	11 (44.0)/14 (56.0)	12 (48.0)/13 (52.0)	0.770**
	Within three months	1 (4.0)/24 (96.0)	0 (0)/25 (100)	0.990*
	Within six months	0 (0)/22 (100)	0 (0)/23 (100)	-
P		< 0.001	< 0.001	
Seizure (yes/no)	At admission	4 (16.0)/21 (84.0)	7 (28.0)/18 (72.0)	0.300**
	Within three months	1 (4.0)/24 (96.0)	0 (0)/25 (100)	0.990*
	Within six months	0 (0)/22 (100)	1 (4.3)/22 (95.7)	0.990*
P		0.090	0.005	
Intra-cranial hemorrhage (yes/no)	At admission	2 (8.0)/23 (92.0)	7 (28.0)/18 (72.0)	
	Within three months	1 (4.0)/24 (96.0)	0 (0)/25 (100)	
	Within six months	0 (0)/22 (100)	0 (0)/23 (100)	
P		0.220	0.001	
Extra-cranial hemorrhage (yes/no)	At admission	1 (4.0)/24 (96.0)	0 (0)/25 (100)	
	Within three months	1 (4.0)/24 (96.0)	1 (4.0)/24 (96.0)	
	Within six months	1 (4.5)/21 (95.5)	0 (0)/23 (100)	
P		0.990	0.360	
Papilledema (yes/no)	At admission	16 (64.0)/9 (36.0)	16 (64.0)/9 (36.0)	
	Within three months	0 (0)/25 (100)	2 (8.0)/23 (92.0)	
	Within six months	0 (0)/22 (100)	1 (4.3)/22 (95.7)	
P		< 0.001	< 0.001	
Death	At admission	0 (0)/25 (100)	0 (0)/25 (100)	
	Within three months	0 (0)/25 (100)	0 (0)/25 (100)	
	Within six months	0 (0)/22 (100)	0 (0)/23 (100)	
P		-	-	

*Fisher's exact test; **Chi-square test; £Cochran test

Discussion

To the best of our knowledge, this is the first double-blind case-control study comparing the outcomes of warfarin, an anti-vitamin K agent, versus rivaroxaban, direct Xa factor inhibitor, in a large population of 50 patients for the treatment of CVT. In the current report, both of the groups were similar in terms of demographic, clinical, and medical information; therefore, the probable confounding role of these data has been eliminated. In the further assessments, we found that both of the groups' neurological performance remarkably improved within six months following acute CVT onset, while the comparisons of the two groups in terms of neurological performance, CVT-related complications, and adverse drug effects were similar.

Heparin injection followed by warfarin is still a mainstay for the treatment of CVT,[15] while significant limitations including requirement of multiple monitoring laboratory tests to set the INR in the range of 2-3, incidence of major bleeding, and diverse drug interactions are the notifying reasons which led to investigation of other oral agents to free the patients from multiple refers to laboratories, and neurologists from the concerns about warfarin-related adverse effects and interactions.[16,17]

A few number of studies have either evaluated the efficacy of rivaroxaban for the treatment of CVT or compared it with warfarin.[15,18,19]

Geisbusch et al. conducted a study on 16 patients with CVT and followed them for the least interval of 8 months. They assessed recanalization status using magnetic resonance angiography (MRA) and neurological performance based on mRS. Among the assessed population, 7 ones (43.75%) underwent rivaroxaban treatment with a daily dose of 20 mg. The excellent overall outcomes were achieved in 93.8% of the patients. Furthermore, all of the patients showed complete or at least partial recanalization regardless of their remedy. The two regimens were not statistically different in terms of clinical profile, neurological performance, and adverse effects. One of the patients under warfarin and two under rivaroxaban treatment presented minor bleeding that was well controlled by reduction of dose.[10] Despite the recommendations for the use of rivaroxaban on the first day of deep vein thrombosis (DVT) anticoagulant therapy without bridging therapy requirement,[20] similar to our study, Geisbusch et al. initiated anticoagulant treatment by heparin bridging therapy, as well.

Anticoli et al. were another group of scientists who assessed the use of rivaroxaban therapy for six patients with CVT. They managed their patients using three types of regimens. Two of the patients were treated with the protocol of seven-day heparin therapy followed by daily 20 mg of rivaroxaban at the time of heparin cessation. The next two ones were primarily treated with heparin bridging therapy with warfarin for 15 days, then only warfarin for the next three months, and eventually, daily 20 mg of rivaroxaban for another three months. The last two ones were treated with 15 mg of rivaroxaban twice daily for 21 days and then, 20 mg once daily, as the protocol of DVT. In this study, a follow-up period of 12 months revealed no recurrence, no major adverse effects, and excellent neurological performance in 100% of the patients. They eventually represented rivaroxaban as an efficacious remedy superior to the other oral anticoagulant agents.[19]

Mutgi et al. were the latter group of scientists who used rivaroxaban in two patients referred with the diagnosis of CVT. Rivaroxaban was initiated without bridging therapy, and the treatment endured for three months. None of the patients represented any complication or bleeding; in addition, a 12-month follow-up of them revealed no recurrence.[21]

Wasay et al. represented the latest theory about the use of new oral anticoagulants versus warfarin for the treatment of CVT through a cohort study. In their report, conducted on 111 patients with CVT among which, 45 ones were treated with new agents (36 rivaroxaban and 9 dabigatran) versus 66 ones under warfarin therapy, they found comparable outcomes of the new agents regardless of their type (either rivaroxaban or dabigatran) versus warfarin, while the complications were fewer both during the six-month treatment period and the follow-up stage.[15]

In summary, similar to the other studies, rivaroxaban was not inferior to warfarin regarding clinical manifestations, neurological performance, and adverse effects. Besides, it does not require several laboratory INR checking and adjustments, but the questions that have not been responded yet are about the necessity of bridging therapy for the treatment of CVT with rivaroxaban and the initial dose of treatment. In order to respond to these questions, further investigations are strongly recommended.

Conclusion

Based on this study, rivaroxaban is an efficacious

agent for the treatment of CVT without remarkable adverse effects.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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