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REVIEW ARTICLE **OPEN ACCESS**

RIVAROXABAN AS A THERAPY IN CEREBRAL VENOUS THROMBOSIS (CVT): A SYSTEMATIC REVIEW

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ABSTRACT

Background: Cerebral venous thrombosis (CVT) can be fatal if untreated. The European Stroke Organization recommends Low Molecular Weight Heparin in the acute phase and oral anticoagulants (VKA) for 3-12 months post-acute to prevent a recurrence. Rivaroxaban, a Direct Oral Anticoagulant (DOAC) inhibiting factor Xa, is associated with reduced risks of fatal bleeding and intracranial hematoma. This systematic review aims to evaluate the efficacy and safety of Rivaroxaban therapy in CVT patients.
Objective: To evaluate the efficacy and safety of Rivaroxaban therapy in patients with cerebral venous thrombosis (CVT), particularly in the post-acute phase, through a systematic review of relevant studies.
Methods: Our review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with an electronic search using PubMed, Cochrane, Sage, Embase, and Ebsco published between 2012 and 2022. This study included patients with CVT above 18 years old, confirmed by radiographic examination.
Results: From 339 studies, we found six studies included, with 113 participants who completed the research program. Major bleeding was 2.26% (n=3). Venous thromboembolism was 1.7% (n=2). Recurrent CVT was 1.7% (n=2). A score of mRS 0-1 was 76% (n=86), mRS score 2 was 2.6% (n=3), and 21 subjects in a study were evaluated with NIHSS. Death was found in 1.7% (n=2), which is still unknown. Recanalization in 6-12 months, both partial and complete, was reported 66.3% (n=75), no recanalization was 1.7% (n=2), and no recanalization evaluation was found 30.9% (n=35).
Conclusion: Rivaroxaban appeared safe and has good efficacy as a therapy in patients with CVT after the acute phase.

Keywords: cerebral venous thrombosis, efficacy and safety, rivaroxaban

Introduction

Cerebral Venous Thrombosis (CVT) is a type of stroke that occurs in approximately 0.5% to 1% of all stroke events.[1] The incidence of CVT has increased over the past few years with increasingly developed radiological tests. CVT has various clinical manifestations, ranging from mild symptoms to headaches (in 83% of patients). Moderate symptoms in the form of signs of intracranial hypertension such as headache with papilledema focal deficiencies such as paresis and aphasia accompanied by seizures, and severe clinical manifestations such as encephalopathy, coma, and status epilepticus. If left untreated, CVT can be life-threatening and potentially fatal.[3-5]

Earlier series of CVT reported mortalities of 30-50% and left untreated; the condition is potentially life-threatening. Recent reports describe mortality of 5-30%.[27-29] CVT is affected by various causative factors that are reversible or non-reversible, including (1) prothrombin mediated like factor V mutations, protein C and S deficiencies, anti-thrombin III deficiencies, and antiphospholipid antibodies, pregnancy, postpartum, malignancy, diseases related to coagulation and complications of brain surgical

interventions (2) inflammatory bowel disease, Crohn's disease, ulcerative colitis and treatment using steroids, sinusitis, trauma.[3-5] Drugs that trigger CVT include oral contraceptive pills (OCP), tamoxifen, and erythropoietin.[3]

So far, the recommended therapy for CVT is anticoagulation unless contraindicated, plus intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) therapy.[8-10] In 2017, the European Stroke Organization recommended the use of Low Molecular Weight Heparin in the acute phase of CVT and oral anticoagulant drugs at some time (3-12 months) after CVT to prevent recurrent CVT and other venous thromboembolic events. Heparin and vitamin K antagonists (VKA) were the basis of VTE prevention and treatment used for over 60 years because they were the only anticoagulants available then.7

Warfarin is a conventional oral anticoagulant, a vitamin K antagonist commonly used to treat blood clotting diseases such as deep vein thrombosis and pulmonary embolism. Warfarin is also used to prevent stroke in people who have atrial fibrillation, heart valve disease, or an artificial heart valve.[11] Vitamin K antagonists have good effectiveness, but vitamin K antagonists require monitoring of food and drug interactions, coagulation status, and dose adjustments to maintain ideal international normalized ratio (INR) values.[7] Monitoring INR levels is affected by factors such as patient age, polytherapy, genetics, herbal consumption, and diet. As a result, oral anticoagulant therapy requires regular monitoring, which can be burdensome for patients and healthcare providers.[10,11]

These limitations prompted the development of direct oral anticoagulants (DOACs), including dabigatran, which inhibits thrombin, and Rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit factor (F)Xa.[7] Direct oral anticoagulants (DOACs) have become an option for treating symptomatic CVT patients over the past ten years and have advantages over warfarin: more predictable pharmacokinetics, no requirement for international normalized ratio (INR) monitoring or daily dose adjustment, and may demonstrate benefit. which is similar in the treatment of acute CVT with lower rates of intracranial hemorrhage. Rivaroxaban is the first oral FXa inhibitor used to prevent and treat CVT.

Rivaroxaban can result in a reduction in the likelihood of fatal bleeding and intracranial hematoma.[4,13,14] Side effects associated with Rivaroxaban therapy are hepatobiliary disorders, allergic and hypersensitivity reactions, leukocytoclastic vasculitis, and alopecia.[15] This systematic review aimed to collect data and evaluate the efficacy and safety of Rivaroxaban as therapy in patients with CVT.

Methods

The authors conducted a systematic search in the databases PubMed, Cochrane, Sage, Embase, and Ebsco for systematic reviews published in the English language literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 2).[25] The search terms used were Cerebral Venous Thrombosis, CVT, and Rivaroxaban, separately and in combination using Boolean logic. The Included studies were published in 2012-2022.

Eligibility Criteria

Articles eligible for review were original research, which was available online and had full text. The methods used in the included studies were randomized control trials and cohort studies. This study discusses CVT patients over 18, as confirmed by radiographic tests such as MRI, CT angiography, CT scan, or DSA. Our exclusion criteria included studies without follow-up data and samples diagnosed with recurrent CVT before being given Rivaroxaban therapy.

Study Selection

The studies that fulfilled the inclusion criteria were retrieved in their complete text form and thoroughly evaluated to determine their eligibility. The full texts underwent screening by three independent reviewers, namely MN, ASA, and AAP. In cases where differences in opinion arose among the reviewers, these disagreements were resolved through in-depth discussion among them. Nevertheless, if the reviewers were unable to reach a consensus after the discussion, the resolution of any remaining disagreements was entrusted to the decision of the first author.

Results Assessment

The findings derived from this systematic review and meta-analysis encompass several key outcomes, namely the incidence of major bleeding, the recurrence of cerebral venous thrombosis (CVT), venous thromboembolism, the modified Rankin scale, recanalization occurring within a period of 6 to 12 months, and mortality rates. For inclusion in our systematic review, studies were required to address a minimum of five out of the six specified outcome criteria that were utilized as essential parameters in the analysis.

Risk of Bias

The quality of bias was assessed using the risk of bias assessment checklist developed by Cochrane (Figure 1).[26]

	Random Sequence Generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Another source of bias
Sara Esmaeili et al, 2021	-	-	-	+	+	-	-
Meraj Fatima et al, 2019	+	+	+	-	-	-	+
Muhammad Maqsood et al., 2021	+	-	-	+	?	+	-
Christina Geisbusch et al, 2014	-	?	-	?	+	+	-
Fariborz et al, 2021	?	-	?	-	?	+	+
Anticoli S, et al, 2016	-	-	+	+	-	+	+

Figure 1. Cochrane Risk of Bias

Results

In the electronic search stage, 339 articles discussed Rivaroxaban as a therapy for cerebral venous thrombosis (CVT). After eliminating duplication and reviewing abstracts, 26 journals were obtained. The authors wrote six journals based on the inclusion criteria in the final results.

Research Characteristics

The authors included six studies with 113 participants who had completed the research program and received Rivaroxaban therapy during the program. A total of 3 studies were retrospective cohort studies. A total of 2 studies were prospective cohort studies. Another study was a double-blinded randomized control trial.

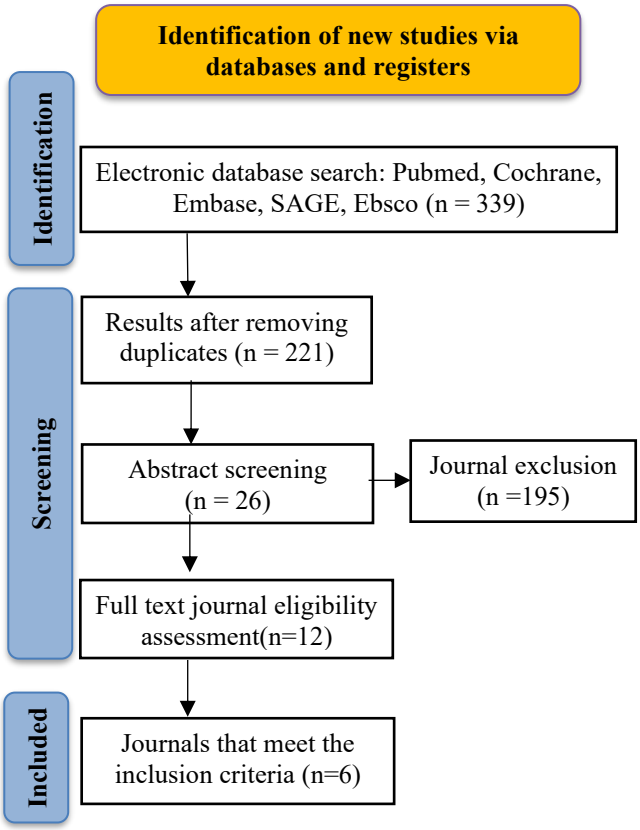

Figure 2. PRISMA Flowchart

Research Characteristics

The authors included 6 studies with 113 participants who had completed the research program and received Rivaroxaban therapy during the program. A total of 3 studies were retrospective cohort studies. A total of 2 studies were prospective cohort studies. Another study was a double-blinded randomized control trial.

Intervention Design

In the 6 included studies, 113 research subjects received Rivaroxaban therapy for 6-12 months. In research by Sara Esmaeili et al, Muhammad Maqsood et al, Christina Geisbusch et al, and Fariborz et al, subjects were divided into 2 groups, namely the group that received Rivaroxaban therapy and the other group received vitamin K antagonist therapy. Meanwhile, in 2 other studies the samples were only grouped into 1 group and given Rivaroxaban therapy (Table 1).

Follow-up

In the 6 included studies, follow-up to determine outcomes in subjects given Rivaroxaban therapy were carried out at months 3, 6, 8, and 12. Outcomes assessed were bleeding, venous thromboembolism, recurrent CVT, death, modified Rankin Scale (mRS), and recanalization 6-12 months. In studies that have a lack of data on outcomes, the risk of bias has been assessed using the Cochrane Checklist Risk of Bias, so that it can be attached for consideration for discussion (Table 2).

Table 1. Journals Included in the Systematic Review

No	Author	Title	Research Design	Intervention	Outcome
1	Sara Esmaeili et al, 2021[16]	Rivaroxaban for the Treatment of Cerebral Venous Thrombosis	Retrospective Cohort Study	The total subjects were divided into 2 groups. A total of 13 patients with CVT were given LMWH or heparin therapy and then continued with warfarin. Meanwhile, in another group, 23 patients diagnosed with CVT were given initial therapy with LMWH or Heparin, then continued with Rivaroxaban. Evaluation is carried out after 12 months.	Rivaroxaban has good efficacy equivalent to vitamin K antagonists. The risk of bleeding in patients receiving Rivaroxaban therapy is not higher than that of vitamin K antagonists.
2	Meraj Fatima et al, 2019[17]	An Observational Study to Evaluate the Effectiveness of Rivaroxaban in the Management of Cerebral Venous Sinus Thrombosis	Retrospective Cohort Study	Patients diagnosed with CVT based on MRV are given Rivaroxaban treatment after the acute phase, for 24-28 weeks, and evaluated at 3 and 6 months. Outcome was assessed from the modified Rankin Scale (mRS)	Rivaroxaban showed promising results.
3	Muhammad Maqsood et al., 2021[21]	Use of Oral Rivaroxaban in Cerebral Venous Thrombosis	Retrospective Cohort Study	The research was conducted in May 2017-May 2018. Patients with a diagnosis of CVT who had passed the acute phase were divided into two groups; 1 group was given Rivaroxaban therapy 20 mg-30 mg/day. In the other group, Vitamin K oral anticoagulant (VKA) was given at 1/3/5 mg/day. The evaluation was carried out at 3, 6, and 12 months.	The clinical results and recanalization of Rivaroxaban therapy patients were quite good. Therapeutic outcomes were acceptable. There were no serious side effects. Rivaroxaban therapy can be a safe therapy option for CVT cases.
4	Christina Geisbusch et al, 2014[2]	Novel Factor Xa Inhibitor for the Treatment of Cerebral Venous and Sinus Thrombosis First Experience in 7 patients	Retrospective Cohort Study	Research data collection was carried out from January 2012- December 2013. The research was carried out on patients with CVT. Patients were divided into two groups: those who received Phenprocoumon (VKA) and novel factor Xa inhibitor (Rivaroxaban) treatment. Follow-up was carried out after 8 months. Outcome assessment using the modified Rankin Scale (mRS) and evaluation of recanalization based on Magnetic Resonance Angiography (MRA).	Rivaroxaban has advantages in terms of metabolism and more practical therapeutic applications. Rivaroxaban therapy has good outcomes and minimal side effects. However, there was no significant difference in VKA and Rivaroxaban therapy results.
5	Fariborz et al, 2021[20]	Evaluation of Rivaroxaban versus Warfarin for the Treatment of Cerebral Vein Thrombosis: A case-control masked study	Double-Blinded Randomized Control Trial Research	A total of 50 patients with CVT were studied from April 2018 to May 2019. Patients were diagnosed based on a CT scan or MRI and then given Rivaroxaban 20 mg/day or warfarin therapy with a dose based on the patient's INR, which was checked once a week. Drug administration was carried out randomly after the administration of enoxaparin therapy in the acute phase. Evaluation was carried out at the 3rd and 6th months of therapy.	Rivaroxaban is effective for CVT treatment without serious side effects.
6	Anticoli S. et al, 2016[4]	Treatment of Cerebral Venous Thrombosis with Rivaroxaban	Retrospective cohort study	This study had a sample of 6 patients diagnosed with CVT who were given Rivaroxaban therapy. Sample data was collected from January 2010 to July 2014. The average duration of administration of Rivaroxaban was 48 weeks. Diagnosis of CVT is based on MRI. Follow-up imaging was performed at 3 and 12 months to assess recanalization. Evaluation was also carried out using the modified Rankin Scale (mRS).	Rivaroxaban has good clinical potential and a safety profile for CVT therapy.

Table 2. Outcomes from Journals Included in the Systematic

No	Writer	Outcome										
		Major Bleeding	Venous thromboembolism	Reccurent CVT	mRS	Death	6 Months Recanalization			12 Months Recanalization		
							Complete	Partial	None	Complete	Partial	None
1	Sara Esmaeili et al, 2021[16]	0	0	1	mRS 0-1: 19 mRS two :3	0	-	-	-	10	2	2
2	Meraj Fatima et al, 2019[17]	2	2	1	mRS 0-1: 29	2	12	17	-	-	-	-
3	Muhammad Maqsood et al., 2021[21]	0	0	0	Evaluation using NIHSS NIHSS 0:20 NIHSS 1-4: 1	0	14	4	3	19	2	-
4	Christina Geisbusch et al, 2014[2]	0	0	0	mRS 0-1: 7	0	4	3	-	-	-	-
5	Fariborz et al, 2021[20]	1	0	0	mRS 0-1:25	0	No recanalization evaluation was carried out.					
6	Anticoli S. et al, 2016[4]	0	0	0	mRS 0-1: 6	0	5		1	2	4	-
	Total	2.26% (n=3)	1.7% (n=2)	1.7% (n=2)	mRS 0-1: 76% (n=86) mRS 2: 2.6% (n=3) NIHSS 0: 17.6% (n=20) NIHSS 1-4: 0.85% (n=1)	1.7% (n=2)	Recanalization 6-12 months partial+complete 66.3% (n=75) No recanalization 1.7% (n=2) Recanalization evaluation was not carried out 30.9% (n=35)					

Discussion

This systematic review and meta-analysis research aimed to determine the efficacy and safety of Rivaroxaban as therapy for cerebral venous thrombosis (CVT) based on research from 2012-2022. The implication of this systematic review and meta-analysis is to provide recommendations for administering Rivaroxaban therapy to patients with CVT who have passed the acute phase.

This systematic review included six journals with a total of 113 participants who had carried out research programs and evaluated using specific criteria to determine treatment results clinically and based on supporting examinations. In a journal written by Sara Esmaeili, it was found that one patient who was given Rivaroxaban therapy experienced a new CVT event within the period of giving Rivaroxaban therapy. It was discovered that the patient reduced the dose of Rivaroxaban without the doctor's permission from 20 mg to 10 mg.[16] Meanwhile, in research by Meraj Fatima, recurrent CVT was also found in 1 patient. Recurrent CVT occurred within 6 months of treatment with Rivaroxaban, but there was no further explanation.[17] Recurrent CVT is prone to occur 24 months after the patient was first diagnosed with CVT.[23] The risk of recurrent CVT increases in patients with a history of venous thrombus, a history of malignancy, malignant hemopathy, polycythemia, and thrombocythemia.[23,24]

In a journal by Meraj Fatima, bleeding occurred in 2 patients.[17] In the Fariborz study, there was an incident of extracranial bleeding in 1 patient during 3 months of treatment with Rivaroxaban.[20] Rivaroxaban has been reported to reduce the likelihood of fatal bleeding and intracranial hematoma. In treating cerebral venous sinus thrombosis, Rivaroxaban can achieve and maintain the ideal international standard ratio (INR) value.[4,14,19] However, in patients given Rivaroxaban therapy who are >65 years old, the risk of gastrointestinal bleeding increases; this should be a concern in therapy monitoring. If bleeding occurs, administration of Rivaroxaban should be discontinued.[22]

The trials show an unexpected increase in gastrointestinal bleeding, especially among patients aged 75 years or over. Prevalence of gastrointestinal

bleeding increases with age and increased risk of gastrointestinal bleeding has been observed in older people when warfarin or novel oral anticoagulants are prescribed concomitantly with antiplatelet agents.[30-33]

In the attached journal, there is research by Meraj Fatima, which included the incidence of venous thromboembolism in 2 patients.[17] Rivaroxaban is a therapeutic option for venous thromboembolism in patients undergoing knee and hip replacement to prevent pulmonary embolism and prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation.[5] Rivaroxaban is also approved by the US FDA for prophylaxis of deep vein thrombosis (DVT) and secondary prevention of venous thromboembolism in patients at risk of VTE.[7] Several factors that influence the occurrence of venous thromboembolism after CVT include gender, age, and a history of thrombophilia, or hypercoagulable status.[2]

There were deaths in 2 patients who were research subjects by Meraj Fatima. In the characteristics of research subjects by Meraj Fatima, subjects with comorbidities such as diabetes (n=3), hypertension (n=5), ischemic heart disease (n=2), chronic kidney failure (n=1), and autoimmune disease (n=7) were found. Meanwhile, it is known that the causes of CVT in Meraj Fatima research subjects were pregnancy/postpartum (n=16), antiphospholipid syndrome (n=7), anemia/other blood disorders (n=2), hereditary thrombophilia (n=1), head trauma (n=2), oral contraceptives (n=2), and smoking (n=1). However, the cause of death was not explained in detail, whether it was related to Rivaroxaban therapy or due to other conditions in the study sample.[17]

Six studies included in this systematic review conducted evaluations on research participants. The results of Rivaroxaban therapy were evaluated by assessing clinical and mRS scores and radiological evaluation to assess recanalization. In research by Sara Esmaeili, 19 subjects had an evaluation score of mRS 0-1 and an mRS score of 2 for as many as three people; the total research sample was 23. Research by Meraj Fatima found subjects with an mRS score of 0-1, as many as 29 people out of the total. 31 sample people. Research by Christina Geisbusch found that all subjects (n=7) had an mRS score of 0-1. In research by Fariborz, it was found that all subjects (n=25) had an mRS score of 0-1. All subjects in the Anticoli study (n=6) had mRS scores of 0-1.[16,17,20,4]

In the journals included in the systematic review, recanalization was found at 6-12 months; both partial and complete recanalization was 66.3% (n=75), no recanalization accounted for 1.7% (n=2), while in 30.9% (n=35) subjects were not evaluated for recanalization. Meanwhile, in Fariborz's research, recanalization evaluation was conducted on less than 25 research subjects.

In the study by Muhammad Maqsood, clinical outcome evaluation was assessed using the National Institutes of Health Stroke Scale (NIHSS) at months 3, 6, and 12. The assessment of the NIHSS score was also carried out when the research subjects were hospitalized. In subjects in the group given Rivaroxaban therapy at admission, a mean NIHSS score of 11 was obtained with a minimum range of 5 and a maximum of 15. Meanwhile, one subject had an NIHSS score with a score range of 1-4. The total number of subjects in Muhammad Maqsood's research was 21 people. At the 3rd, 6th, and 12th months of evaluation, subjects given Rivaroxaban therapy obtained an NIHSS score of 0 in 20 people.[21]

In conclusion, the six journals stated that Rivaroxaban has good therapeutic efficacy and safety for therapy in patients with cerebral venous thrombosis (CVT).

The shortcomings of this systematic review research are the limited inclusion of journals using the double-masked randomized control trial method, journals with larger sample sizes, and the still need for journals that state significant differences regarding the efficacy of administering Rivaroxaban and other therapies such as CVT therapy.

Conclusion

In conclusion, the six journals stated that Rivaroxaban has good therapeutic efficacy and safety for therapy in patients with cerebral venous thrombosis (CVT) after the acute phase.

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