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COMPARISON OF WARFARIN AND RIVAROXABAN IN TREATMENT OF CEREBRAL VENOUS SINUS THROMBOSIS

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Abstract:

Background: *Cerebral venous sinus thrombosis (CVST) refers to a distinct stroke type accounting for 0.5% to 1% of all strokes. Standard treatment for CVST with warfarin is limited by the need for continuous monitoring of anticoagulation with INR. A simple solution to some of these issues could be administration of an oral anticoagulant that does not require laboratory monitoring yet is effective as a single agent for the treatment of acute venous thromboembolism and for continued treatment. Rivaroxaban is one such medicine that can solve this problem.*

Methodology: *It was an open label interventional clinical quasi-controlled Trial conducted at Department of Neurology, Sir Ganga Ram Hospital/Fatima Jinnah Medical University, Lahore for duration of 20 months from January, 2017 to August, 2018. Patients were randomly divided into two groups (Group Warfarin, and Group Rivaroxaban) using computer generated random number table. Treatment started with low molecular weight heparin (Enoxaparin 1mg/kg body weight/day) for 5 to 7 days depending upon improvement in neurological status. Group Rivaroxaban was given Rivaroxaban 15mg twice a day for 21 days followed by 20 mg daily for 12 weeks. Group Warfarin was given warfarin starting with a dose of 5mg and titrating to a target INR 2.0 to 3.0. Patients were followed over 6 months.*

Results: *Overall 30 patients were included in the study. Group Warfarin includes 15 patients and group rivaroxaban also includes 15 patients. Detailed characteristics of all patients in both groups have been summarized in table I.*

Female patients were 11 (73.33% in group warfarin and 10 (66.66%) in group rivaroxaban.

Overall, warfarin and rivaroxaban both showed efficacy in treatment of cerebral venous sinus thrombosis without any significant difference betweem two groups (P-Value= 0.543). Table II. Overall efficacy was upto 90%.

Conclusion: *In sum, this study demonstrates that rivaroxaban is effective in managing CVST similar to warfarin. Rivaroxaban can be preferred treatment option owing to its safety as no monitoring is needed. Warfarin if monitored adequately and INR maintained within target range can be equally safe in this regard.*

Key Words: *Cerebral Venous Sinus Thrombosis, Warfarin, Rivaroxaban.*

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INTRODUCTION:

Cerebral venous sinus thrombosis (CVST) refers to a distinct stroke type accounting for 0.5% to 1% of all strokes.[1,2] The clinical spectrum of CVST ranges from non-specific or mild symptoms of headache, visual complains, focal neurologic deficits, seizures or coma. Cerebral venous thrombosis (CVT) affects approximately 15 people per million annually and represents 0.5% of all stroke. [3,4]. The current guidelines recommend initiation of treatment with heparin followed by oral anticoagulants with Vitamin K antagonists namely warfarin for 3 to 6 months after confirmation of diagnosis with computed tomography (CT) or magnetic resonance (MR) venography. [5]
New oral anticoagulants (NOACs) that inhibit factor Xa or thrombin directly have been developed. Rivaroxaban has been approved as therapy for treatment of deep vein thrombosis(DVT) and prevention of systemic embolism in patients with atrial fibrillation since December, 2011. [6]. The EINSTEIN studies and Einstein-Extension showed a noninferior efficacy for rivaroxaban compared with enoxaparin plus a vitamin K antagonist in patients with peripheral deep vein thrombosis [8,9] In ROCKET AF trial, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism in patients with atrial firillation. [1]

Apixaban and rivaroxaban have been shown to be non-inferior to warfarin for the treatment of deep vein thrombosis and pulmonary embolism. [10,11]. However, only case reports and small case series have described their use in patients with cerebral venous sinus thrombosis. Standard treatment for CVST with warfarin is limited by the need for continuous monitoring of anticoagulation with INR. This presents a challenge to outpatient management since treatment with a vitamin K antagonist requires laboratory monitoring and dose adjustment and may be complicated by drug and food interactions. After the first year, the annual risk of major bleeding associated with vitamin K antagonists is 1 to 2%. [18] Consequently, the balance between the risks and the benefits of continued therapy remains a subject of debate, despite the high long-term risk of recurrent venous thromboembolism. A simple solution to some of these issues could be administration of an oral anticoagulant that does not require laboratory monitoring yet is effective as a single agent for the treatment of acute venous thromboembolism and for continued treatment.12 Rivaroxaban is one such medicine that can solve this problem. The current study has been conducted to compare the efficacy of these two medicines to make recommendations for treatment of CVST with a reliably safe medicine like rivaroxaban.

MATERIALS & METHODS:

It was an open label interventional clinical quasi-controlled Trial conducted at Department of Neurology, Sir Ganga Ram Hospital/Fatima Jinnah Medical University, Lahore for duration of 20 months from January, 2017 to August, 2018. Total 30 patients were enrolled in the study. Sampling Technique was non-probability consecutive sampling. Patients of both genders with ages between 14 and 70 years having cerebral venous sinus thrombosis (Patients with headache, new onset neurological deficit or seizures having evidence of cerebral venous thrombosis on magnetic resonance venography) were included in the study. Patient anticipated to require invasive procedure (e.g., lumbar puncture, thrombectomy, hemicraniectomy) prior to initiation of oral anticoagulation, Impaired renal function (Creatinine clearance < 30 mL/min), Pregnancy, Lactating mother, Bleeding diathesis or other contraindication to anticoagulation, Any concurrent medical condition requiring mandatory antiplatelet or anticoagulant use, Concomitant use of strong CYP3A4 inducers (e.g., ongoing use of dilantin, carbamazepine, HIV protease inhibitors) or CYP3A4 inhibitors (e.g., diltiazem, systemic ketoconazole), severe or fatal comorbid illness that will prevent improvement, or cannot complete follow up were excluded from the study. Informed consent was taken from each participant of the study. Patients were randomly divided into two groups (Group Warfarin, and Group Rivaroxaban) using computer generated random number table. Treatment started with low molecular weight heparin (Enoxaparin 1mg/kg body weight/day) for 5 to 7 days depending upon improvement in neurological status. Group Rivaroxaban was given Rivaroxaban 15mg twice a day for 21 days followed by 20 mg daily for 12 weeks. Group Warfarin was given warfarin starting with a dose of 5mg and titrating to a target INR 2.0 to 3.0. Patients were followed over 6 months.

Primary outcome measure was recanalization at 24 weeks on MRV (no recanalization, partial recanalization, complete recanalization). Secondary outcome measure was achievement of modified Rankin Scale 0-1 (Annex I).

Patients were followed for bleeding events over 6 months. Symptomatic intracranial bleeding during 6 months, Major extracranial bleeding (bleeding in a critical area or organ, including intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a drop in hemoglobin by 20 g/L or more, leading to transfusion

of 2 or more units of whole blood or red cells) at 6 months, Clinically relevant non-major bleeding(Epistaxis, mucosal bleed, conjunctival hemorrhage, heavy menstrual bleeding, ecchymosis) during 6 months.

Data was collected using a standardized Performa by investigators. All the collected information was transferred to SPSS version 20 and analyzed. Mean and standard deviation were calculated for all quantitative variables like age and modified rankin scale. Frequency and percentages were calculated for all qualitative variables like gender, recanalization at 6 months, symptomatic intracranial bleeding during 6 months, major extra cranial bleeding, clinically relevant non major bleeding during 6 months. Efficacy was defined as modified Rankin scale of 0-1. Efficacy was compared in both groups using chi square test. P value of <0.05 was taken as significant. Independent sample t test was applied to see efficacy of treatment in group A and group B. P value of <0.05 was taken as significant.

RESULTS:

Overall 30 patients were included in the study. Group Warfarin includes 15 patients and group rivaroxaban also includes 15 patients. Detailed characteristics of all patients in both groups have been summarized in table I.

Female patients were 11 (73.33% in group warfarin and 10 (66.66%) in group rivaroxaban.

Overall, warfarin and rivaroxaban both showed efficacy in treatment of cerebral venous sinus thrombosis without any significant difference betweem two groups (P-Value= 0.543). Table II. Overall efficacy was upto 90%.

Table I: Characteristics of the Study Population

	Group warfarin n = 15	**Group rivaroxaban n = 15**	**P-Value**
Age	35.87+10.789	31.47+9.187	0.249
Gender			
Male	4 (26.6%)	5 (33.3%)	0.690
Female	11 (73.33%)	10(66.66%)	
Modified Rankin Scale at presentation	3.73±0.799	3.47±0.743	0.649
Modified Rankin Scale at Follow up	0.40±0.83	0.47±1.06	0.505
Complete Recanalization	8 (53.33%)	6 (40%)	0.706
Partial Recanalization	6(405)	7 (46.67%)	
No Recanalization	1(6.67%)	2(13.33%)	
Major Extracranial Bleeding	0	0	
Major Extracranial Bleeding	0	0	
Minor extracranial bleeding	1(6.67%)	3 (205)	

Table II: Comparison of Efficacy in the both groups

		Efficacy		Total
		Yes	No	
Group	Warfarin	14 (93.335)	1 (6.675%)	15
	Rivaroxaban	13 (86.66%)	2 (13.335)	15
Total		27 (90%)	3 (10%)	30 (100%)
Chi square test		0.370		
p-Value		0.543		

DISCUSSION:

Cerebral venous sinus thrombosis is life-threatening condition though uncommon with an incidence of 2 to 5 /million/year although it is variable between different studies.13 the standard of care in routine is initiation of treatment with heparin (both low molecular weight heparin and unfractionated heparin can be used) followed by warfarin with a target INR of 2.0 to 3.0.14 when there is resistance to treatment, endovascular interventional treatmen is also helpful. [15]

Rivaroxaban, an orally active, direct factor Xa inhibitor, is effective in the prevention and treatment of venous thromboembolism. It does not require laboratory monitoring and has no food interactions and only a few drug interactions., [16,17,18]

Current treatment i.e., heparin followed by warfarin for CVST is limited by the need for laboratory monitoring and dose adjustment and may be complicated by drug and food interactions. Annual risk of major bleeding associated with vitamin K antagonists is 1 to 2%. A simple solution to some of these issues could be administration of an oral anticoagulant that does not require laboratory monitoring yet is effective as a single agent for the treatment of acute venous thromboembolism and for continued treatment. [12]

This was a small scale study including only 30 patients of cerebral venous sinus thrombosis conducted in Neurology ward. The study concluded that warfarin and rivaroxaban both are very effective in treating cerebral venous sinus thrombosis and rivaroxaban is no inferior to warfarin for treatment of cerebral venous sinus thrombosis.

In previous epidemiological studies, incidence of cvst is higher in females than males. In a systemic review, the ratio of Female to male was 2.79 in cvst. It is similar to our sstudy in which female population is more than two times than male population. [19]

There are very few studies comparing warfarin and rivaroxaban. One such study found that both drugs are equally effective in treating cerebral venous sinus thrombosis. Overall efficacy was upto 90%. Complete recanalization was upto 50% with partial recanalization also 50%. These results also support our study which also concluded that rivaroxaban is noninferior to warfarin in treatment of CVST and complete recanalization was 53.33% in group warfarin and 40% in group rivaroxaban with no significant difference. [20]

A study conducted by Anticolli S etal., showed that rivaroxaban is effective in treatment of CVST and at three months, an excellent outcome (mRS of 0 to 1) was observed in 100% of patients and complete or partial recanalization in 83%. At 12 months, an excellent outcome was observed in 100% of patients and complete (33%) or partial recanalization (67%) in all cases. There were no bleeding complications

(major, clinically relevant nonmajor, or minor) or recurrent thrombotic events during followup and all patients were alive at last study visit. These results also support the results of our study which showed no major bleeding and only 1 minor bleeding in group warfarin and 3 in group rivaroxaban. [21]

Warfarin is a time tested drug for treatment of CVST and it is very cost effective. It needs continuous monitoring with PT-INR and if monitoring is not done there is always a risk of major intracranial and extracranial haemorrhage. Rivaroxaban is a novel oral anticoagulant with activity against activated Factor X and needs no monitoring. Hence it is an asset for the patients and doctors. It is more costly than warfarin.

Keeping in view, the small sample size of the study and the scarcity of data on the subject especially with rivaroxaban, large scale randomized controlled studies are needed to convincingly establish and compare the efficacy of these medications.

CONCLUSION:

In sum, this study demonstrates that rivaroxaban is effective in managing CVST similar to warfarin. Rivaroxaban can be preferred treatment option owing to its safety as no monitoring is needed. Warfarin if monitored adequately and INR maintained within target range can be equally safe in this regard.

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