CLINICAL OUTCOMES OF CEREBRAL VENOUS SINUS THROMBOSIS TREATED WITH RIVAROXABAN

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Abstract

Objective: Cerebral venous sinus thrombosis (CVST) is an uncommon subtype of stroke. Anticoagulation with heparin and warfarin is the recommended treatment. Direct Oral Anticoagulants (DOACs) have shown efficacy and safety in other thrombotic conditions and are being investigated for use in CVST. Our study aims to investigate the clinical outcomes of patients with CVST treated with Rivaroxaban.

Methods: This prospective observational study was carried out in Rehman Medical Institute for 20 months (August 2021 to April 2023). Patients aged 18-60 years with clinically stable CVST were enrolled in study. Patients were treated with heparin followed by rivaroxaban, and follow-up visits were scheduled at 3, 6 and 12months. The primary outcome included recanalization, secondary outcomes included bleeding episodes, non-resolution of CVST, time to recanalization, recurrence of VTE, and functional recovery of the patient. Information was recorded in predefined proforma, and anticoagulation duration was based on guidelines.

Results: The study included 18 patients with CVST. The majority of patients were female (83.3%) with a mean age of 37.55±11.77 years. The cause of CVST was undetermined in most cases (61.1%), followed by postpartum (22.2%) and pregnancy (11.1%). Multiple sinuses were involved in half of the cases. At 3 months follow-up, full recanalization was achieved in 38.9%. At 6 months follow-up, full recanalization was seen in 81.8% of patients. No clinically relavant bleeding event was observed. There was no recurrence of CVST at 1-year follow up. All patients achieved full recovery NIHSS 0.

Conclusion: Rivaroxaban is a safe and efficacious treatment option in CVST.

Keywords: Cerebral Venous sinus thrombosis, rivaroxaban, anti-coagulant

Introduction

Cerebral venous sinus thrombosis (CVST) is a relatively rare cause of stroke that can results from complete or partial blockage of main cerebral venous sinuses or cortical veins.[1] Only 1% of all strokes are registered as CVST strokes, with an annual incidence ranging from 0.22 to 1.57 per 100,000. There is a known geographical disparity in its incidence, with a reported imaging prevalence of 11.05%, 95%CI [8.54-13.56%] from a Pakistani study.[2] CVST patients are typically younger than those with arterial types of strokes with female predominance.

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The 2014 American Heart Association/American Stroke Association (AHA/ASA) guidelines state that anticoagulation is suitable for patients with acute CVST, even in the presence of hemorrhage in venous infarct. The guidelines recommend initial anticoagulation with heparin in anticoagulant doses, followed by oral Warfarin.[3,4]

Direct Oral Anticoagulants (DOACs) are a novel group of drugs, such as Dabigatran, Rivaroxaban, and Edoxaban, that directly inhibit factor Xa or thrombin. They have been proved to have similar efficacy as of conventional anticoagulation with a 50% reduction in bleeding risk in atrial fibrillation (AF), deep vein thrombosis (DVT), and pulmonary embolism (PE).[5,6] However**,** their role is currently under discussion in cerebral venous thrombosis.

A small RCT by Geisbusch et al. reported Rivaroxaban has the same efficacy as of Warfarin in treatment of CVST.[7] The VTE-AL trial proved DOACs to be non-inferior to Enoxaparin in treating VTE-AL.[8] A systematic analysis by Lee et al and a meta-analysis

comprising six studies described DOACS are noninferior to Warfarin in terms of recanalization, and clinical recovery and safety outcomes. [9,10] These findings suggest that DOACs could be a potential alternative to VKAs due to their better safety profile, targeting a single site in the coagulation cascade, and not requiring INR monitoring. While clinical trials are awaited to make DOACs a part of CVST treatment guidelines.

A local study showed that Rivaroxaban is a highly effective alternative to warfarin, with clinical and radiological recovery observed in 50% of patients at 3 months and 38% at 6 months.[11] Another two researcher from Pakistan have also described the similar efficacy and safety of oral rivaroxaban as of vitamin K anticoagulant (warfarin) in CVST.[12,13] These findings suggest that Rivaroxaban could be a suitable option for the treatment of CVST, avoiding the concerns associated with warfarin.

In our setting, lack of INR testing standardization, patient/family compliance and awareness issues, and drug/food interactions causing fluctuations in INR are important factors that lead to Warfarin related complications frequently. In a study from Karachi Pakistan described that 65.7% patients on warfarin therapy were not aware of its side effects and its food/drug interaction. More over 75% patients were not aware of INR testing during Warfarin therapy.**[14]** DOACs can be safe alternative of Warfarin in our setup. Our study aims to investigate the clinical outcomes of patients with CVST treated with Rivaroxaban, including vein recanalization, time to recanalization, hemorrhagic events, and recurrence.

Methods

This prospective observational study was conducted at the Neurology/Stroke Unit of Rehman Medical Institute, Peshawar from August 2021 to April 2023. The study received approval from the institute's ethical committee, and all participants provided written informed consent before joining the study.

The diagnosis of cerebral venous sinus thrombosis (CVST) was confirmed through magnetic resonance venography brain in all cases. The study enrolled patients aged between 18-60 years who were diagnosed with thrombosis of cerebral veins and were clinically stable. Clinically stable CVST was defined with a Glasgow Coma Scale (GCS) score of > 10/15. Patients who had major bleeding episode in last 6 months, suffering from current or active malignancy or comorbid conditions like renal failure, heart failure, and liver cirrhosis were excluded. Moreover, CVST associated with sepsis or central nervous system infection was also not included in study. All patients were started on LMWH 1mg/kg twice daily and switched to rivaroxaban 15mg twice daily on the third day. After 21 days, the dose of rivaroxaban was changed to 20mg once daily. Follow-up visits were scheduled at 3, 6 and 12months, and any bleeding or thrombotic events were recorded. Follow-up imaging with magnetic resonance venography was performed at 3 months and repeated at 6 or 12 months in cases of partial resolution at 3 months. The duration of anticoagulation was decided based on guidelines depending upon the provoking factor of CVST.

The primary outcome of the study was the recanalization rate, which was assessed by MRV at 3 and 6-month follow-ups by two consultant radiologists. The secondary outcome included any bleeding episode, non-resolution of CVST, time to recanalization, recurrence of VTE, and functional recovery of the patient.

Major bleeding was defined as life threatening bleed that has led to a significant drop in hemoglobin level requiring transfusion of at least 2 units red blood cells. Hemorrhage into a critical anatomical site like intracranial or retroperitoneal cavity was also considered as major bleed. Minor bleeding was categorized into two categories: clinically relevant and clinically non-relevant bleeding. Clinically relevant bleeding was defined as overt bleeding that is less than a major bleeding but needs medical intervention. All other bleeds were considered clinically non relevant.

Functional recovery was assessed using the "National Institute of Health Stroke Scale (NIHSS)" scoring, which ranges from 0 (minimum) to 42 (maximum). The score of 0 represents as an excellent clinical outcome; 1–4 score represents minor disability; 5–15 shows moderate disability; 16–20 represents moderate to severe disability; and 21–42 represents severe disability. The score was recorded at follow-up visits.

All information was recorded in a predefined proforma.

Data Analysis

Data were analyzed using SPSS (version 24) software. The percentage of recanalization, defined as partial or complete resolution of CVST, was calculated. Time to recanalization was also analyzed. Clinical outcomes were measured using the National Institute of Health Stroke Scale (NIHSS) staging, with percentages calculated for each score category. Additionally, frequencies and percentages of recurrent thrombosis, complications, and deaths were described

Results

The study enrolled a total of 18 cases, consisting of 3 (16.7%) male and 15 (83.3%) female participants, with an average age of 37.55±11.77 years.

Out of these 18 patients, the precipitating factors for CVST remained unclear in 11 patients, accounting for 61.1% of the cases. In four patients (n=4), CVST occurred postpartum, accounting for 22.2% of the cases, while two patients (n=2) experienced it during pregnancy/gestation accounting for 11.1% of the cases. In one patient (n=1), the underlying cause for CVST was attributed to a hypercoagulable state, accounting for 5.6% of the cases.

In the 18 patients diagnosed with cerebral venous sinus thrombosis (CVST), the sagittal sinuses were found to be involved in (n=8) 8 patients, accounting for 44.4% of the cases, while transverse sinus involvement was seen in only one patient (n=1) , accounting for 5.6% of the cases. Interestingly, almost half of the cases, n=9 (50%), were found to have multiple sinus involvement.

At 3 months follow-up on MRV Imaging, full recanalization was seen in n=7 patients (38.9%) at 3 months and n=9 patients (81.8%) at 6 months.

Further analysis revealed that full canalization was achieved at 3 months in patients who had single sinus involvement as compared to multiple sinuses, however the difference remained statistically insignificant (p 0.14).

Among the precipitating causes, most of the cases of Pregnancy related CVST showed full recanalization at 3 months as compared to other causes (p 0.02).

Table 2: Sinus involvement and precipitating factors in relation to recanalization outcomes in patients with cerebral venous sinus thrombosis.

		Full recanalization at 3months	Partial recanalization at 3months	P value
Sinus involvement	Single sinus involved	5 (71.4%)	4 (36.4%)	0.14
	Multiple sinuses involved	2 (28.6%)	7 (63.6%)	
Precipitating factor	Pregnancy related	5 (71.4%)	1(9.1%)	0.02
	Hypercoagulable state	0(0.00%)	1 (9.1%)	
	Undetermined	2 (28.6%)	9 (81.8%)	

Our results showed that bleeding was not observed in any of the patients during therapy. Furthermore, none of the patients included in the study experienced a recurrence of CVST during the follow-up period. All patients recovered completely at 6months NIHSS being 0.

Discussion

CVST mainly affects young to middle-aged adults. A study by Khan MWA and Chu Z et al. has described age in early 30's.[16] Relatively higher ages (mean 41 years) of CVST have been reported in post covid CVST.[17] A large meta-analysis comprises of 554 CVST cases in British Columbia from 2000 to 2017 described mean age of CVST as 50.9%.[18] The discrepancy in this regard may be due to etiological and racial differences in studies.

(CVST) predominantly affects females, as observed in our present study. This finding is consistent with Alvis-Miranda HR et al. and Roeder et al.[19,20] However, there are also studies that have reported a more equal distribution of gender among CVST patients.[18,21] Another study by Prabhu et al. in 2022 reported 70% male predominance.[22]

These discrepancies in gender distribution can be due to the etiological factors of CVST, few of them are more common in male gender e.g., smoking, polycythemia, hyperhomocystinemia, while thrombophilia and hormone dependent venous thrombosis predominant in females.

CVST carries a multifactorial etiology. A 2014 study by Zia A et al. reported that in Pakistan the most common precipitating factor in their CVST cases was infection (18%), followed by postpartum state (17%)[23] Alivs-Miranda HR et al. found that in developed countries congenital thrombophilia was the most common precipitating factor.[20] The 2020 systematic review by Komro J et al. described exogenous estrogen hormone therapy (EEHT) (54.5%) and pregnancy or puerperal patients (36.4%) to be common risk factors.[24] These findings suggest that multiple factors can contribute to the development of CVST, and that the underlying etiology may vary depending on the population studied. In our study large number of patients had indeterminant risk factor to CVST. The reason may be the unavailability of appropriate investigations facilities and resource limited services.

CVST can affect different sinuses. Several studies have investigated the sinuses involved in it. About 73% transverse sinus involvement was reported to involve in a study by Shahid et al. [21] Xiuli Chu et al. described that 58.4% cases had multiple sinus involvement. [25] Another study by Khan MWA et al. reported multiple sinus involvement in 66.6% of cases.[16] This finding is consistent with the results of our present study.

Recanalization of the affected sinuses is a crucial factor in determining the clinical outcome of patients with CVST. In a systematic review from 2022 by Nepal at al. complete recanalization was seen in half of the patients at 3months with both rivaroxaban and warfarin[26]. Relatively less patients in our study achieved full recanalization at 3months and the majority needed 6months anticoagulation for full resolution. In this regard our results are supported by a Systemic review by Arauz A et al. in which complete recanalization was achieved in 32.4% at 3 and 49.7% at 6months.[27] A study from Pakistan showed that only 39% patients being treated with rivaroxaban were able to achieve full recanalization even at 6 months.[28] Possible reasons for these discrepancies include demographic and racial differences, magnitude of sinus involvement, precipitating factor for CVST and treatment strategies.

The bleeding risk associated with the treatment of CVST varies. The 2022 study by Jian YY et al. reported a risk of minor bleeding with rivaroxaban (7.9%) .[29] The study by Fatima M et al. (2021) reported bleeding events in 6% of patients with cerebral venous sinus thrombosis (CVST) receiving rivaroxaban.[12] In contrast, in our study, none of the patients developed bleeding while receiving anticoagulation therapy. Similarly, a study by Esmaeili et al. (2021) found no cases of major bleeding in their study.[30] It should be noted that bleeding risk with anticoagulation therapy for CVST is a potential complication and requires careful monitoring especially in case of Warfarin, however the negligible risk of bleeding with DOACs makes them the choice of agent for treatment of CVST.

CVST related to pregnancy has a better prognosis and lower mortality compared to CVST caused by other factors. A study conducted by Meng SH et al. (2021) supports these findings, revealing that pregnancy-related CVST has a lower mortality rate and a better outcome than non-pregnancy-related CVST.[31] This is in favour of our results of good prognosis and recovery of pregnancy related CVST. This may be explained by the fact that pregnancy related CVST is often detected and treated earlier due to increased awareness and surveillance in pregnant patients. Also, pregnancy related CVST is commonly associated with transient hypercoagulable states, which may be easier to identify and manage compared to other risk factors.

CVST recurrence has been documented in literature especially in patients with non-modifiable risk factors like thrombophilia etc. Fatima et al. reported 3% of the study population that developed recurrent CVST within a span of six months.[28] However, in our study none got recurrence in 1 year follow up.

Taken together, these findings suggest that newer oral anticoagulants such as rivaroxaban can offer safe and effective options for the management of CVST, with potentially fewer complications and better patient outcomes compared to traditional therapies such as warfarin.

Our study has certain limitations. Firstly, it's a single center study comprises of small population. Secondly, we have described the outcome but have not compared rivaroxaban with Warfarin which is still a recommended treatment for CVST. Thirdly, we took only clinically stable patients that may have

underestimated the bleeding complications and functional outcome.

Conclusion

Rivaroxaban is an effective and safe alternative to Warfarin in treating CVST. Complete recanalization is achieved in majority patients at 6 months. Single sinus disease and Pregnancy related CVST achieved recanalization at 3 months. All patients achieved full functional recovery. No patient developed bleeding complication or recurrence over 1 year follow up. Further studies are needed to validate our findings and bring Rivaroxaban in place of Warfarin in treatment of CVST.

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