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A Review Article on Safety and Efficacy of Newer Oral Anticoagulants in the Treatment of Cerebral Venous Sinus Thrombosis

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ABSTRACT

CVST (Cerebral Venous Sinus thrombosis) is an uncommon and complex illness with gender-specific origins and a wide range of clinical manifestations. It is also a rare kind of stroke that can be lethal if misdiagnosed or treated late. The reasons for this vary across industrialized and developing countries. It is distinguished by a clinical spectrum that is very varied, difficult diagnosis, various etiologies, and a prognosis that necessitates exceptional medical skills and a high suspicious score. When compared to vitamin K antagonists, NOACs had a roughly 50% decreased incidence of intracerebral hemorrhage. Direct oral anticoagulants have been the first-line medications used to treat this illness, but in this expanding world, newer oral anticoagulants such as Apixaban, Dabigatran, Rivaroxaban, and Edoxaban are being employed.

KEYWORDS: Cerebral venous Sinus Thrombosis, Newer oral anticoagulants, Factor X A, Apixaban, Dabigatran, Rivaroxaban, Edoxaban

INTRODUCTION

Cerebral venous Sinus thrombosis (CVST) or Cerebral Venous Thrombosis (CVT) is an uncommon condition characterized by thrombosis of the brain's veins and sinuses, most often the superior sagittal sinus. [1] Cerebral venous Sinus thrombosis (CVST) is a clinical condition in which the venous drainage of the brain is obstructed. This can result in cerebral ischemia or bleeding. [2] It is a rare cause of stroke, yet it is associated with high morbidity and death. It contributes for 0.5%-1% of all strokes, with the majority of cases occurring in young people. CVST is three times more frequent in women than in males and can be fatal if left untreated.

It is an uncommon consequence of hypercoagulable conditions such as Pregnancy, Lupus anticoagulant syndrome, Systemic lupus erythematosus, Crohn's disease, Ulcerative colitis, Malignancies, and Oral contraceptive pill usage. It most typically affects young individuals, particularly women, although it can also affect the elderly.

RISK FACTORS

Multiple risk factors have been linked to CVT etiology, although in many cases, the cause is unknown. Modifiable and non-modifiable risk factors include:

a) Prothrombic conditions such as factor V mutation, protein C and S deficiency, Ant thrombin III deficiency, and Antiphospholipid antibody;
b) Inflammatory conditions such as inflammatory bowel disease, Crohn's disease, and ulcerative colitis;

c) Pregnancy, puerperium, malignancies, and other conditions with hypercoagulable states;
d) Sinusitis
e) Some drugs, such as oral contraceptives (OCPs), tamoxifen, erythropoietin, and heparin. [3]

CLINICAL PRESENTATION

The signs and symptoms range from localized neurological deficits to mental status changes. Cerebral venous thrombosis can cause a variety of symptoms as a result of an underlying pathophysiological process that involves the occlusion of the cerebral venous sinuses. A thrombus in the cerebral venous sinus might reduce absorption of cerebrospinal fluid (CSF) and hence raise venous and capillary pressure. This can then lead to vasogenic edema and reduced perfusion, which can lead to ischemic damage and rupture of the blood-brain barrier (BBB) with elevated intracranial pressure (ICP). [3]

Neuroimaging verifies the diagnosis of CVD (Cerebrovascular Disease), with current treatment dependent on severity. Brain CT scans and MRV are employed as imaging modalities, with magnetic resonance imaging being the most prevalent. [4]

TREATMENT

NOACs have emerged as a potential alternative to Warfarin in thrombotic and thromboembolic disorders, and some research shows that NOACs, when compared to Vitamin-K antagonists, reduce the risk of severe and fatal hemorrhages. NOACs are being researched for their effectiveness, short half-life, oral administration, and decreased monitoring of prothrombin time, APTT, and INR. In certain thromboembolic circumstances, these drugs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, provide an alternative to systemic anticoagulation. Dabigatran inhibits factor Xa, preventing thrombin generation, whereas rivaroxaban inhibits factor Xa, preventing thrombin production. NOACs have emerged as a potential alternative to Warfarin in thrombotic and thromboembolic disorders, and some research shows that NOACs, when compared to Vitamin-K antagonists, reduce the risk of severe and fatal hemorrhages. More study with bigger samples is required to assess the efficacy of these innovative oral anticoagulants in the treatment of CVST. [1]

The current recommended treatment for CVT patients is heparin or Low Molecular Weight Heparin (LMWH) followed by an oral anticoagulant. [5] The most commonly recommended drug is warfarin. However, because of the requirement for continual monitoring, the danger of bleeding, and variable bioavailability owing to dietary interaction, achieving and maintaining adequate INR is frequently problematic. [6]

Dabigatran selectively and competitively inhibits thrombin (factor 2a), whereas rivaroxaban, apixaban, and edoxaban block factor Xa, which connects the intrinsic and extrinsic routes in the coagulation cascade and functions as a rate-limiting step in thrombin production. [3] Over the last decades, Novel Oral Anticoagulants (NOACs) such as Rivaroxaban might offer a convenient alternative to Warfarin in some thrombotic and thromboembolic disorders. [7, 8]

DISCUSSION

NOVEL ANTICOAGULANTS IN CVT

Nguyen TH, Ngo TM et al., conducted a study on the topic "The novel oral anticoagulants for the treatment of cerebral venous thrombosis". The trial included 32 Vietnamese patients with CVT, 72% of whom were female; 15 were given rivaroxaban and 17 were given dabigatran. Magnetic resonance venography was used to evaluate recanalization. At 180 days of follow-up, all patients had achieved at least partial recanalization, and half had achieved full recanalization, with no bleeding problems.[4]

SAFETY AND EFFICACY OF DIRECT ORAL ANTICOAGULANTS

Bose G, Graveline J et al., conducted a study on "direct oral anticoagulants in treatment of cerebral venous thrombosis; a systematic review". The purpose of the research was to demonstrate that, despite oral anticoagulants' advantages over standard therapy, current recommendations do not include them in the treatment of CVT. Included in the study are 279 individuals who received DOAC for CVT. dabigatran (41%), rivaroxaban (47%), apixaban (10%), and edoxaban (2%), And conventional therapy was administered to 315 individuals. The study found that, despite variations in treatment schedule and dosage, DOAC shows sufficient safety and efficacy. [9]

Lurkin A, Derex L et al., conducted a study on the topic "Direct oral Anticoagulants for the treatment of cerebral venous thrombosis". The study is a retrospective observational study that took place between January 2016 and March 2018 at two French university hospitals. The trial included 41 patients, 25 of whom were given VKAs and 16 of whom were given direct oral anticoagulants. The study indicated that the effectiveness and safety of direct oral anticoagulants in CVT therapy looked promising. [8]

SAFETY OF DABIGATRAN IN CVT

Chaturbedi A, Thakur J et al., conducted study on "Dabigatran, a direct thrombin inhibitor, as the first-line treatment for cerebral venous thrombosis". The research included seven adult patients who reported cerebral bleeding caused by CVST from dural venous sinus blockage. Dabigatran was administered as the primary treatment for around 6 months, and it resulted in total recanalization in five patients and partial recanalization in two. During DTI (Direct Thrombin Inhibitor), no patient experienced enlarged hematomas. The study revealed that DTI is a safe and effective main therapy technique for individuals with CVST. [10]

Ferro JM, Coutinho JM et al., conducted a study on the "safety and efficacy of Dabigatran Etexilate vs Dose adjusted warfarin in patients with cerebral venous thrombosis". The aim of this research is to examine the effectiveness and safety of dabigatran etexilate against dosage modification in avoiding recurrent VTEs in CVT patients. The trial included 120 CVT patients who were randomly assigned to one of two therapy groups. 60 were assigned to dabigatran and 60 to dose-adjusted warfarin. The research revealed that there were no recurring VTEs and that the risk of bleeding was comparable with both drugs. This study found that dabigatran and warfarin are both safe and effective at preventing recurrent VTEs in CVT patients. [11]

SAFETY OF RIVAROXABAN, APIXABAN AS WELL AS COMBINATION OF BOTH IN CVST

Maqsood M, Imran Hasan Khan M et al., conducted a study on "the use of oral rivaroxaban in cerebral venous". The study's goal was to evaluate the safety of oral anticoagulants against warfarin. The research included 45 CVT patients who were placed into two therapy groups. 21 patients were given rivaroxaban, while 24 were given warfarin. Overall recanalization was accomplished in 18 patients using rivaroxaban and 20 with warfarin, according to the research. The study indicated that rivaroxaban is a safe alternative for CVT; nevertheless, bigger randomized controlled trials will have an impact on validity. [5]

Iyer RS, Ramakrishnan TC et al., conducted a study on "is it safe to treat cerebral venous thrombosis with oral rivaroxaban without heparin". The study's goal is to demonstrate that newer oral anticoagulants, such as rivaroxaban, are progressively becoming the cornerstone of therapy for systemic thrombosis. The trial comprised 20 individuals who began using rivaroxaban and were followed for an average of 6 months. According to the study, full recanalization was observed in 12 patients and partial recanalization was observed in 8

patients. According to the findings of the study, in clinically stable CVT rivaroxaban is safe and effective and may be taken without prior heparin medication. It also reduces the length of hospitalization, lowering the expense of therapy. [12]

Rao SK, Ibrahim M et al., conducted a study on "Apixaban for the treatment of cerebral venous Thrombosis". The study's goal was to evaluate the safety and efficacy of newer anticoagulants. Apixaban was given to the patients in this trial. Apixaban was well accepted by the patients, and no bleeding problems occurred. Apixaban may be a safe and effective therapeutic option for CVT. [13]

Dong X, Liu X et al., conducted a study on "clinical efficacy of conventional Heparin Anticoagulation combined with Apixaban in the treatment of patients with cerebral venous Thrombosis and its effect on serum D Dimer and FIB expression". The purpose of the trial was to examine the clinical efficacy for conventional heparin anticoagulation when combined with apixaban in the treatment of individuals with cerebral venous thrombosis. The trial included 157 consecutive CVT patients, 5 of whom got conventional medication and 62 of whom received Apixaban therapy. The study indicated that the combination of Apixaban and heparin is effective and safe in the treatment of CVT. [14]

COMPARISON BETWEEN VITAMIN K ANTAGONISTS AND NEWER ORAL ANTICOAGULANTS

Yaghi S, Shu L et al., conducted a study on "direct oral anticoagulant safer than warfarin with cerebral venous thrombosis". The study is a retrospective observational analysis of 845 individuals treated for cerebral venous thrombosis between 2015 and 2020, with about 33% receiving direct oral anticoagulants, 51.8% receiving warfarin alone, and 15.1% receiving both at different periods. When compared to warfarin, direct oral anticoagulants were associated with a reduced risk of significant hemorrhage, according to the study. [15]

Shahid R, Ishaque N et al., conducted an observational study "comparing the safety and efficacy of conventional anticoagulants versus new oral Anticoagulants in the management of cerebral venous sinus Thrombosis". The purpose of the study was to assess the safety and efficacy of traditional anticoagulants to novel oral anticoagulants in the treatment of cerebral venous sinus thrombosis. The research included 36 patients, 15 of whom were men and 21 of them were women. The study shows that novel anticoagulants are at least as effective as traditional anticoagulants in the treatment of CVST. Their effectiveness was discovered to be almost identical. [16]

CONCLUSION

NOACs offer therapeutic advantages in treating cardiovascular disease (CVD) with minimal side effects. They have predictable pharmacokinetics, linear pharmacodynamics, and a dose-response relationship. They do not require laboratory testing and require prospective evaluation with randomized controlled trials. Rivaroxaban improves recanalization and reduces hospital stays, while Apixaban is well-tolerated and safe for CVT patients. Dabigatran helps avoid recurrent VTEs, and direct oral anticoagulants have a decreased risk of serious bleeding compared to warfarin. Current guidelines do not recommend using novel OACs for CVT treatment, but studies can pave the way for larger clinical trials, producing more statistically safe and significant data. This could revolutionize CVT treatment, especially for remote people in developing countries without access to tests like prothrombin time or activated partial thromboplastin time (PT/APTT) and INR.

Abbreviations

CVST: Cerebral Venous Sinus Thrombosis
NOACs: Newer Anticoagulants
OCPs: Oral Contraceptives
CSF: Cerebrospinal Fluid
BBB: Blood Brain Barrier
ICP: Intracranial Pressure

CVD: Cerebrovascular Disease
MRV: Magnetic Resonance Venography
LMWH: Low Molecular Weight Heparin

Declaration by Authors

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