Is there a Place to New Oral anticoagulants for Cerebral Venous Thrombosis? ¿Hay lugar para nuevos anticoagulantes orales para la trombosis venosa cerebral? Existe lugar para novos anticoagulantes orais para trombose venosa cerebral?

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Abstract

Cerebral Venous Thrombosis (CVT) is an important neurologic emergency among adults, mainly in women. It is associated with genetic or acquired risk factors, and elevated estrogen exposure stands out. The principal symptom is a headache, characterized to be intense, progressive, and worsening with the Valsalva maneuver. The diagnosis is mostly based on D-dimer, which has a high negative predictive value, helping to exclude the hypothesis, and magnetic resonance imaging (MRI), which can confirm the suspicion by presenting some specific signs such as the dense triangle sign (clot inside the sinus), cord sign (thrombosed cortical or deep vein), and empty delta sign. The treatment was mostly based on unfractionated heparin (UH), low molecular weight heparin (LMWH), and Warfarin; however, now direct-acting oral anticoagulants (DOACs) are assuming an important role in this scenery. Here we present a brief literature review searched at Pubmed and Embase concerning the best drug method to treat CVT and two successful cases in young women patients managed with LMWH for a week, followed by a six-month treatment with Rivaroxaban.

Keywords: Cerebral venous thrombosis, stroke, diagnosis, treatment, Low molecular weight heparin, direct-acting oral anticoagulants.

Resumen

La trombosis venosa cerebral (TVC) es una emergencia neurológica importante entre los adultos, principalmente en las mujeres. Se asocia a factores de riesgo genéticos o adquiridos, destacando la exposición elevada a estrógenos. El síntoma principal es el dolor de cabeza, que se caracteriza por ser intenso, progresivo y que empeora con la maniobra de Valsalva. El diagnóstico se basa principalmente en el dímero D, que tiene un alto valor predictivo negativo, ayudando a excluir la hipótesis, y en la resonancia magnética (RM), que puede confirmar la sospecha al presentar algunos signos específicos como el signo del triángulo denso (coágulo). dentro del seno), signo del cordón (vena cortical o profunda trombosada) y signo del delta vacío. El tratamiento se basó principalmente en heparina no fraccionada (UH), heparina de bajo peso molecular (HBPM) y warfarina; sin embargo, ahora los anticoagulantes orales de acción directa (ACOD) están asumiendo un papel importante en este escenario. Aquí presentamos una breve revisión de la literatura buscada en Pubmed y Embase sobre el mejor método farmacológico para tratar la TVC y dos casos exitosos en pacientes mujeres jóvenes manejadas con HBPM durante una semana, seguida de un tratamiento de seis meses con Rivaroxaban.

Resumo

A Trombose Venosa Cerebral (TVC) é uma importante emergência neurológica entre adultos, principalmente em mulheres. Está associada a fatores de risco genéticos ou adquiridos, destacando-se a exposição elevada ao estrogênio. O principal sintoma é a cefaleia, caracterizada por ser intensa, progressiva e piorar com a manobra de Valsalva. O diagnóstico é baseado principalmente no dímero D, que tem alto valor preditivo negativo, ajudando a excluir a hipótese, e na ressonância magnética (RM), que pode confirmar a suspeita apresentando alguns sinais específicos como o sinal do triângulo denso (coágulo dentro do seio), sinal do cordão (cortical trombosado ou veia profunda) e sinal do delta vazio. O tratamento baseou-se principalmente em heparina não fracionada (HNF), heparina de baixo peso molecular (HBPM) e varfarina; entretanto, agora os anticoagulantes orais de ação direta (DOACs) estão assumindo um papel importante neste cenário. Apresentamos aqui uma breve revisão da literatura pesquisada no Pubmed e Embase sobre o melhor método medicamentoso para tratar TVC e dois casos de sucesso em pacientes jovens tratadas com HBPM por uma semana, seguida de tratamento de seis meses com Rivaroxabana.

1. Introduction

Cerebral Venous Thrombosis (CVT) is a neurological emergency. It is less frequent than ischemic and hemorrhagic vascular accidents. This condition has an incidence that varies from

0.22/100 to 1.32/100 in worldwide neurological centers. The prevalence of CVT in Latin America is not well established due to the lack of robust studies; most of them are only case reports or series of cases. The specific prevalence of CVT is more common than bacterial meningitis in adults and affects more young patients. Women are more affected than men [Ferro and Canhão (2014)]. CVT presents itself in several ways, which makes quick diagnosis difficult. Fortunately, this is rarely seen as an ischemic syndrome; when it occurs, the cerebral cortex is much more affected than the brain stem. Regarding risk factors for CVT, oral contraceptives, pregnancy, puerperium, infections, and malignant diseases stand out [Ferro et al. (2004)]. However, any pro-thrombotic state, whether genetic or acquired, can cause such pathology. Despite the clinical picture, there is great variability in its presentation, which can be acute, subacute, or chronic, although this is much less frequent.

Headache is the most frequently observed symptom and is sometimes the only one. It is usually holocranial, severe, progressive, worsening with the Valsalva maneuver, typical of intracranial hypertension [Cumurciuc et al. (2005)]. Transient or permanent loss of vision, eye pain, focal deficit with or without seizures can occur [Jacobs et al. (1996); Cakmak et al. (2004)]. After the advent of magnetic resonance imaging (MRI) with venography window (MRV), the diagnosis became easier, although the tomography shows very suggestive signs of CVT, such as the dense triangle sign (clot inside the sinus), cord sign (thrombosed cortical or deep vein), and empty delta sign [Buonanno et al. (1978)]. To help the diagnosis, D-dimer levels can be measured. They are increased in patients with CVT; however, they can show normal values in patients with isolated headaches [Crassard et al. (2005)]. D-dimer has a high negative predictive value around 97% and a low sensitivity around 85% [Dentali et al. (2012b)].

The management of this condition is usually based on anticoagulant agents. In the past years, it was restricted to unfractionated heparin (UH), low molecular weight heparin (LMWH), and Warfarin; however, now DOACs are assuming an important role on the scene. In this study, we intended to make a literature review of the best way to manage CVT cases, considering the treatment effectiveness and safety, and also report two CVT cases treated with DOACs with positive outcomes.

2. Methodology

In the present article, we conducted a review of literature on the standard treatment of Cerebral Venous Thrombosis (CVT). To gather the newest information concerning the use of direct-acting oral anticoagulants (DOACs) compared to unfractionated heparin (UH), low molecular weight heparin (LMWH), and Warfarin, we performed a search on Pubmed and Embase using the terms ”Cerebral Venous Thrombosis” AND (”Treatment” OR ”Therapeutics” OR ”Therapy”). The stipulated dates of publication were articles from 2017 to 2022. We chose these dates based on the fact that the European Stroke Organization had already published guidelines for the diagnosis and treatment of cerebral venous thrombosis, synthesizing information about CVT treatment in a high-quality meta-analysis. After the initial search, we selected articles by title and included those that involved the clinical management of CVT in adults.

3. Similarities and Differences

The warfarin is the older and more used anticoagulant in medical practice. It is a coumaric found in plants (Melilotus officinalis, Fabaceae). After this discovery, many synthetic drugs with anticoagulant properties are produced. Warfarin is transformed in the liver and is eliminated through urine and feces. There are many substances and drugs that interact with warfarin, and the availability depends on many factors that include liver and kidney function, gender, weight, age, genetic factors, and adherence to treatment. That is why many physicians and patients have difficulty handling this drug.

In a simplified way, warfarin, a vitamin K antagonist, interferes with the carboxylation of several factors necessary for the coagulation pathway, making them ineffective (factors II, VII, IX, X, and protein C and S). It reduces or inhibits the action of vitamin K and decreases the release of coagulation factors.

On the other side, the new oral anticoagulants (NOACs) or direct-acting oral anticoagulants (DOACs) started to be used in medical practice in 2010 with dabigatran, a direct thrombin inhibitor. Since then, others have appeared, acting as a bound and free factor-Xa inhibitor: rivaroxaban, apixaban, edoxaban, and betrixaban [Gosselin et al. (2019)]. Initially, they were approved for secondary prophylaxis in Stroke associated with non-valvular atrial fibrillation (FA), the treatment and secondary prophylaxis of venous thromboembolism (VT), and primary prophylaxis of VT after some surgeries. The DOACs have some properties that facilitate the handling of the treatment.

4. The treatment

The main objective of the treatment of CVT is to reestablish the venous flow of the brain, thus allowing the improvement of symptoms and decreasing the risk of death. Obviously, the symptoms resulting from thrombosis must be treated simultaneously, as is the case with seizures, infection, and dehydration if it occurs.

The first effective treatment for CVT was described in the late 1930s by Stansfield, a British gynecologist. He described the use of heparin in a patient with puerperium CVT [Silvis et al. (2017)].

Since then, heparin has been used as medication in the acute phase of the disease. However, some authors opposed its use due to the risk of intracranial hemorrhage (ICH) [Cumurciuc et al. (2005); Dentali et al. (2012a)]. Another dilemma is the use of unfractionated heparin (UH) or low molecular weight heparin (LMWH).

Unfractionated heparin has been used for a long time, but after the appearance of low-weight heparin, it has been used more due to greater convenience, a minor risk of bleeding, and the lack of activated partial thromboplastin time (PTTa) dosage for correction [Coutinho et al. (2010)]. The advantage of UF is the fact that the PTTa) normalizes within 1–2 h after discontinuation of the infusion if complications occur or surgical

intervention is necessary.

The EFSN guideline recommends the use of UH or LMWH in CVT cases even with uncomplicated intracerebral bleeding (level B recommendation, according to the Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004, considered as probably effective, ineffective, or harmful).

5. Oral anticoagulation

Along with heparin, the anticoagulants are first-choice medications for the treatment of CVT and should be continued after the acute phase of the disease. After anticoagulation in the acute phase, oral anticoagulation should be maintained. Vitamin K antagonists are the most commonly used today, as long as there is no patient contraindication. Warfarin is the oldest drug used for this purpose. In the same context of anticoagulation, DOACs are successful in treating patients with atrial fibrillation, later in deep venous thrombosis, and pulmonary thromboembolism. DOACs, compared to warfarin, have similar efficacy and less risk of bleeding [Hankey et al. (2014); van Es et al. (2014)].

In view of this scenario, the use of rivaroxaban and dabigatram had been tried to treat cerebral venous thrombosis. In the first, there was no major bleeding or recurrent cerebral thrombotic phenomena, and in the second, there were good results in 87% of treated patients and the presence of recanalization in 80% of them [Geisbüsch et al. (2014); Mendonça et al. (2015)].

Anticoagulation should be performed for 3 to 6 months if the cause is reversible, as in pregnancy, puerperium, and infection, and 6 to 12 months in the case of idiopathic CVT. In patients with mild thrombophilia, that is, isolated thrombophilia, treatment should be 6 to 12 months, while in patients with combined thrombophilia or recurrent intra- or extra-cranial thrombosis, treatment should be continued for life [Ferro and Canhão (2014)].

6. Clinical Evidence

Considering the small prevalence of Cerebral Venous Thrombosis and the relatively short time of DOACs in the market, there is little significant scientific evidence about their application in this context.

The European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis was published in 2017, and through a systematic review, treatment recommendations for CVD were gathered. As a result, they do not recommend using DOACs for the treatment of CVT, especially in the acute phase. Although the quality of evidence is very low, and the strength of recommendation is weak, considering that all studies were observational with a high risk of Bias.

Twelve articles were selected and analyzed, published after the European Stroke Organization, and it was observed that there were no major differences between DOACs and warfarin regarding efficacy and risks of complications. Here we describe a brief resume of the articles with a larger number of patients.

The study conducted by Ferro (2019) "Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis, A Randomized Clinical Trial," was published in 2019. 120 patients with CVT were randomized, and 60 were treated with dabigatran, and 60 with warfarin. Although only 109 patients completed the treatment (53 dabigatran and 56 warfarin), in both groups, no major bleeding events happened, there was only one episode of genitourinary bleeding in a patient of the Dabigatran group. The study concluded that the risk of recurrent bleeding in patients with CVT who received dabigatran or warfarin was low. A similar study was conducted by Pan (2021) "Efficacy and safety of rivaroxaban in cerebral venous thrombosis: insights from a prospective cohort study." It evaluated patients with CVT, 33 were treated with Rivaroxaban, and 49 with warfarin. There were no bleeding events in both groups, and during a 6-month follow-up, 87.9% of the rivaroxaban group and 77.6% of the warfarin group obtained recanalization.

A Single-Center Retrospective Evaluation of the Use of Oral Factor Xa Inhibitors in Patients With Cerebral Venous Thrombosis was published by Powell (2021), studied 271 patients, 89 were treated with warfarin, 11 with enoxaparin, 7 with apixaban, and 12 with rivaroxaban. It was concluded that there were no significant differences observed in secondary terms outcomes. Adds to the evidence that apixaban or rivaroxaban may be an alternative to warfarin or enoxaparin in long-term treatment of CVT. However, It's important to consider that the group treated with DOACs was significantly smaller than the one treated with Warfarin.

Another interesting study "New oral anticoagulants versus warfarin for cerebral venous thrombosis: a multi-center, observational study" made by Wasay (2019) analyzed 66 patients on warfarin, 35 on rivaroxaban, and 9 on dabigatran. There were only 6 bleeding patients, 2 from DOAC group and 4 from the Warfarin group, also there were no recurrence of thrombosis. In conclusion, both medications were considered safe and effective, although it wasn't a randomized study, and the radiological follow-up was not performed with most patients.

Dong et al (2021) published a study with 62 patients treated with apixaban and 95 treated with warfarin. Interestingly, the patients had better therapeutic effects using apixaban, that is a cure rate of 41.9% and a significantly improved in 35.48% compared to the group using warfarin (9.47% cured and 23.16% had significantly improved, ($p = 0.02$).

Nepal et al (2022) published a meta-analysis evaluating the safety and efficacy of the use of DOACs in the follow-up treatment of CVT. It was selected not only studies in which there were a control group comparing DOACs efficacy with warfarin but also observational studies with no control group, only the one in use of DOACs. The population of the studies had different age ranges, including one article with a pediatric group. In the analysis of the comparative studies, the DOACs and the warfarin group had a similar positive outcome. In the studies with no comparative group, the recanalization rates were also promising.

Yagui et al (2022) performed a multicenter retrospective study with patients with CVT. The participants were divided

into three different groups, one treated only with DOAC (33%), another treated with warfarin (51.8%), and the last one with both drugs at different times. 845 patients were included, and the conclusion was that all groups had close outcomes, but the DOAC group had a lower risk of hemorrhage (p=0.02).

7. Opinion

Regarding the selected recent studies, the use of DOACs in the management of CVT is a plausible option. Compared to the use of warfarin, the risks of bleeding and their efficacy in preventing new thrombotic events were very similar. Also, DOACs present advantages such as not requiring international normalized ratio monitoring, rapid onset, and shorter half-lives. Although there is still a lack of studies with a larger number of patients to make statistically more relevant comparisons between anticoagulants, it will probably be fulfilled in the next few years.

8. Case reports

1. Female, 35 years old, in regular use of oral contraceptives, presented a progressive and pulsatile headache with severe intensity and vomiting without nausea. Evolved with paresthesia and weakness in the right arm. An angiography brain MRI was performed, which showed thrombosis in the left transverse and sigmoid sinus, left internal jugular vein, and a small cortical frontal vein. She was treated in the first week with LMWH 1mg/Kg twice daily, and after that, with Rivaroxaban 15mg twice daily for three weeks. After this time, the treatment was changed to Rivaroxaban 20 once a day for six months. Another brain MRI was performed 3 months after the incident and revealed a significant reduction of the thrombus in all affected sites. In the following year, another MRI was made (14 months from the event) and revealed thrombosis control with a discreet filling failure at the proximal portion of the transverse sinus compatible with residual thrombosis.

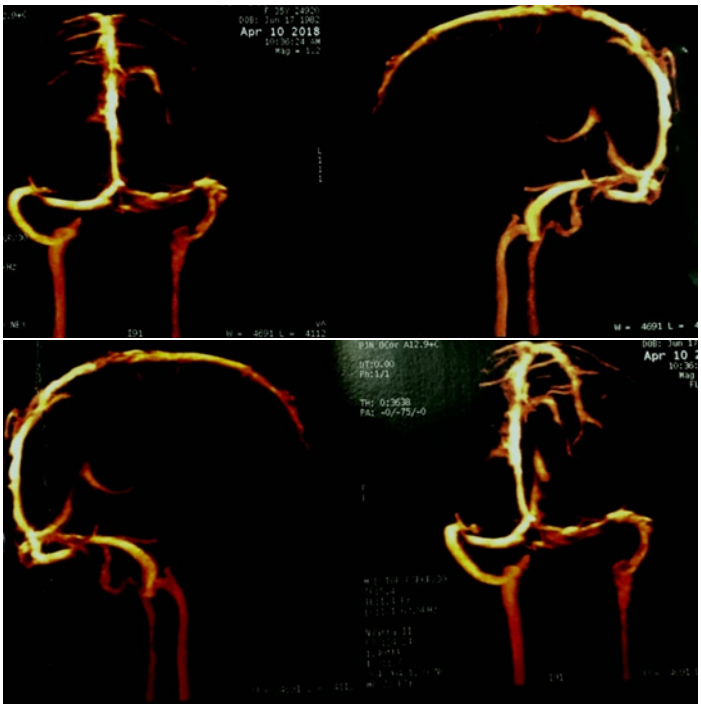

Figure 1: First brain angiography MRI

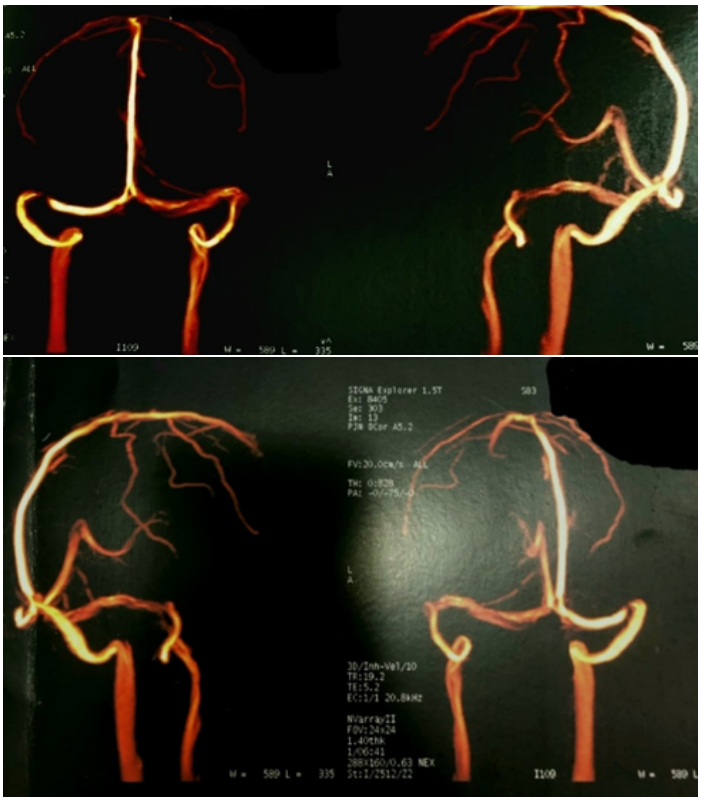

Figure 2: Second brain angiography MRI

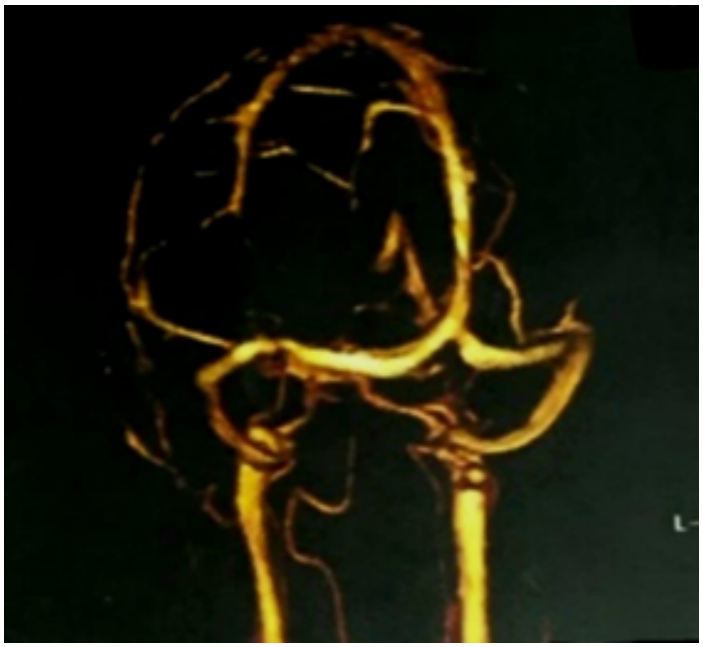

Figure 3: Third brain angiography MRI

2. A 34-year-old female presented with a severe headache associated with seizures, subsequently developing motor and speech deficit (dyslalia) on the right side. She was taken to the ICU where she underwent a volumetric T1 brain angiography MRI with an emphasis on the venous phase on May 8, 2019. The MRI revealed the following findings: filling defects affecting the left internal jugular vein, compatible with chronic venous thrombosis. She was treated with physiotherapy and simultaneously administered LMWH 1 mg/kg twice daily for 3 days and Rivaroxaban 15 mg twice daily. After 3 weeks, the treatment was changed to Rivaroxaban 20 mg once a day for six months.

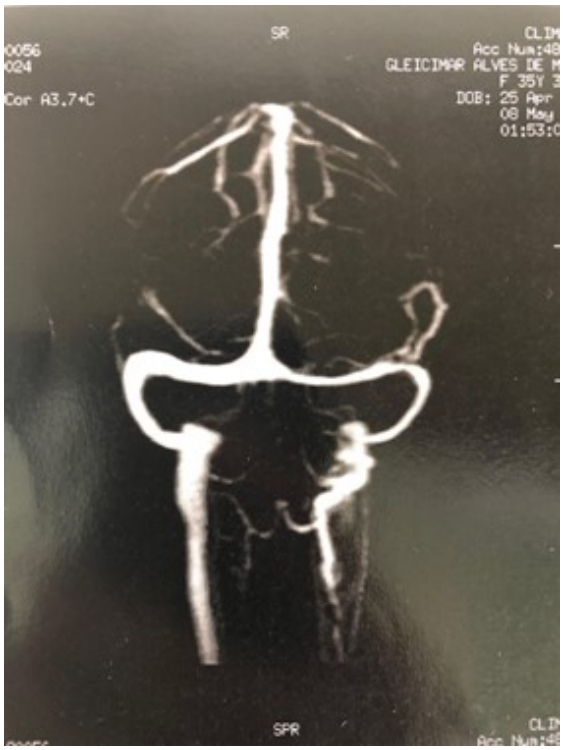

Figure 4: Brain angiography MRI

9. Conclusion

The CVTS is a neurological emergency that must be treated with caution, and one must be aware of possible complications, including ischemia and, especially, cerebral hemorrhage, which can lead to irreversible sequelae and even death. Thrombosis treatment with UF or LMWH can be performed, preferably with the second option. Full anticoagulation for as long as necessary; we already know that warfarin is a safe, effective, and recognized option. Treatment with DOACs in the future, after studies with larger populations, may show efficacy and safety equal to warfarin but with less need for INR control.

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