CEREBRAL VENOUS THROMBOSIS

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To assist health care professionals in the management of cerebral venous thrombosis (CVT).

BACKGROUND:

The cerebral venous system is comprised of both cerebral cortical veins and venous sinuses. CVT refers to thrombosis affecting either (or both) of these sites. CVT is rare, with an incidence of approximately 1.3 per 100,000 person-years and accounting for less than 1% of stroke syndromes. In contrast with pulmonary embolism (PE) and deep vein thrombosis (DVT), CVT primarily affects younger individuals, with median age of 37 years. Women (particularly those of childbearing age) are three times more likely to be affected than men. Most individuals (90%) present with headache, usually severe, and sometimes with accompanying features of intracranial hypertension (decreased visual acuity, papilledema), seizures, focal neurologic changes (stroke), or encephalopathy/coma. Thirty to fifty percent of patients develop concomitant intracranial hemorrhage (ICH) secondary to venous infarction. Forty percent of individuals with CVT develop seizures. This complication occurs most often in those with focal venous hemorrhage.

General risk factors for CVT include heritable and acquired thrombophilias, pregnancy, hormonal therapy, malignancy (especially hematologic malignancies), systemic infections, collagen vascular diseases, including vasculitic disorders (e.g. systemic lupus erythematosus, granulomatosis with polyangiitis, and Behcet's disease) and inflammatory bowel disease. Local risk factors include head trauma, neurosurgery, spinal procedures, and regional infection (e.g. meningitis, otitis, mastoiditis). In less than one quarter of cases, no apparent cause is found.

CVT mortality has decreased steadily over the last few decades, likely due at least in part to earlier diagnosis, and is estimated between 5% and 10%. Approximately 80% of patients will recover completely or with minor deficits, some suffer from chronic symptoms like fatigue, headache, and difficulties concentrating. Recurrence appears to be uncommon at less than 10%; however, the quality of data supporting this estimate is modest.

DIAGNOSIS OF CEREBRAL VENOUS THROMBOSIS:

Neuroimaging is required to diagnose CVT and may also demonstrate juxtacortical hemorrhage, cerebral edema, and rarely hydrocephalus. Most patients are imaged initially with computed tomography (CT) and magnetic resonance imaging (MRI), both of which have similar accuracy for CVT. Non-contrast CT has lower sensitivity. Consequently, the reference standard tests, MR-venography (MR-V) and CT-venography (CT-V), should be performed in patients with a high suspicion for CVT. However, CT-V is less sensitive for CVT and inferior for visualizing venous hemorrhagic infarcts within the brain parenchyma.

MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS:

Given the uncommon nature of CVT, recommendations are based on limited randomized data and observational cohort studies. The primary purpose of treatment is to prevent mortality from venous infarction and cerebral herniation due to increased intracranial pressure (ICP). The general management approach consists of: 1) anticoagulant therapy, 2) management of increased ICP, and 3) seizure management.

Patients with CVT are at risk of sudden decompensation and, therefore, should be managed initially in an intensive care setting. Involvement of Neurology and Hematology/Thrombosis services is recommended.

1. Anticoagulant therapy

   Given the high prevalence of concomitant ICH and weak/moderate level of evidence for anticoagulation, the risks and benefits of anticoagulant therapy should be carefully weighed, considering individual patient circumstances.

   - Anticoagulation with therapeutic dose low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH) is recommended for acute treatment of CVT, even in the presence of ICH. This is based on three small randomized trials in which heparin (LMWH or UFH) were compared with placebo and subsequent meta-analysis of these studies which suggested that anticoagulation was associated with a reduction in death or dependency. No increase in ICH was seen in individuals who received anticoagulants. LMWH may result in fewer hemorrhagic complications, including in those presenting with ICH, lower hospital mortality and better functional prognosis. Intravenous UFH may be more appropriate if surgical intervention is being considered or if immediate reversibility is a consideration.
   - After the acute setting, long-term anticoagulation with vitamin K antagonists such as warfarin (target INR 2.0-3.0) or LMWH is recommended.
   - Data with the direct oral anticoagulants (DOACs) consist of small case series and one exploratory trial. The RE-SPECT CVT trial randomized 120 patients with CVT to dabigatran 150 mg twice daily or warfarin after 5 to 15 days of UFH or LMWH. There were no recurrent VTE events, with low rates of major bleeding in each group. These results are exploratory, and several other trials are planned or ongoing (Clinicaltrials.gov – NCT03178864, NCT03191305, NCT03127448). As such, there is insufficient evidence to recommend the use of these agents in this setting.

2. Management of increased intracranial pressure (ICP)

   - Approximately 5% of patients may present with, or develop, decreased level of consciousness or coma due to increased ICP. Early mortality from transtentorial herniation may occur despite anticoagulant therapy.
   - In circumstances of neurologic deterioration or radiographic evidence of mass effect, urgent neurosurgical consultation is warranted for consideration of decompressive craniectomy. Endovascular therapy with mechanical thrombectomy may also be considered when there is neurologic deterioration despite medical therapy.

3. Seizure management
    - Guidelines support the early initiation of anti-seizure therapy after single or multiple seizures. Referral to a neurologist is indicated. Beware of potential drug-drug interactions with anticoagulants and anti-seizure medications.
    - There is no evidence supporting the use of prophylactic anti-seizure therapy in those who have not developed seizure.

4. Risk factor management
    - Provoking factors, including hormonal therapies, should be discontinued. Lifestyle modifications including smoking cessation should also be encouraged.
    - While heritable and acquired thrombophilias are risk factors for CVT, their relevance and implications for duration and choice of anticoagulation are uncertain; therefore, these tests are not routinely recommended.

DURATION OF THERAPY:

- The optimal duration of anticoagulation in CVT has not been established. Observational studies suggest that the recurrence risk of CVT is low after stopping anticoagulants. Recommendations for duration have been extrapolated from data for DVT and PE and should be based on the patient's individual circumstances.
- CVT in the context of a reversible provoking factor should generally be treated for 3-6 months. In individuals in whom CVT was unprovoked, at least 6-12 months of anticoagulation is suggested. Individuals who have recurrent CVT, prior venous thromboembolism or in whom there is an ongoing provoking factor should be considered for extended anticoagulant therapy with periodic reassessment for bleeding risk, as should those without high risk features for bleeding but are uncomfortable with estimated risks of recurrence associated with anticoagulant discontinuation.
- Data about the risk of CVT during a subsequent pregnancy and the impact of thrombosis prophylaxis on that risk are very limited. In the absence of robust data, it is reasonable to prescribe antepartum and postpartum prophylaxis to pregnant women with a prior history of CVT and no contraindication for anticoagulation.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- Pulmonary Embolism (PE): Treatment
- Unfractionated Heparin, Low Molecular Weight Heparin, and Fondaparinux
- Venous Thromboembolism: Duration of Treatment
- Warfarin

REFERENCES:

Coutinho JM. Cerebral venous thrombosis. J Thromb Haemost 2015;13(suppl 1):S238-S244.

Coutinho J, et al. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database Syst Rev 2011;(8):CD002005.

Coutinho JM, et al. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. Stroke 2010;41:2575-2580.

De Bruijin SF and Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke 1999;30:484-488.

Dentali F, et al. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood 2006;107:2766-2773.

Dentali F, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. J Thromb Haemost 2012;10:1297-1302.

Ferro, JM, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis – endorsed by the European Academy of Neurology. Eur J Neurol 2017;24(10):1203-1213.

Ferro JM, et al. Safety and efficacy of dabigatran etexilate vs. dose-adjusted warfarin patients with cerebral venous thrombosis: a randomized trial. JAMA Neurol 2019;76(12):1457-1465.

Rao SK, et al. Apixaban for the treatment of cerebral venous thrombosis: A case series. J Neurol Sci. 2017;381:318-320.

Saposnik G, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:1158-1192.

Silvis SM, et al. Risk factors for cerebral venous thrombosis. Semin Thromb Hemost 2016;42:622-631.

Silvis SM, et al. Cerebral venous thrombosis. Nature Rev Neurol 2017;13(9):555-565.

Xu W, et al. The performance of CT versus MRI in the differential diagnosis of cerebral venous thrombosis. Thromb Haemost. 2018;118(6):1067-1077.

Date of version: 17Jan2020