Review Article

Heparin in the treatment of Cerebral Venous Thrombosis

Saad Shafqat, Ayeesha K. Kamal, Mohammad Wasay
Department of Medicine (Neurology), Aga Khan University Medical College, Karachi.

Abstract

Cerebral venous thrombosis (CVT) is a potentially life-threatening condition requiring rapid diagnosis and urgent treatment. Heparin anticoagulation is the time-honoured treatment, and is advocated in all cases of CVT, irrespective of etiology or presence of haemorrhage. The supportive evidence is largely observational; data from randomized placebo-controlled trials shows a nonsignificant trend favouring heparin. Current practice is to begin heparin (unfractionated or low-molecular weight) immediately on confirmation of the diagnosis. Newer anti-thrombotic agents such as ximelagatran may offer advantages over heparin and need to be investigated in the treatment of CVT.

Introduction

Thrombosis of the cerebral veins and sinuses (cerebral venous thrombosis, or CVT) has been recognized as a distinct pathologic entity for over 150 years.[1] The disorder is not infrequently encountered in clinical practice - a busy inpatient neurology service can typically see at least a few cases per year. For example, in a large prospective, observational study across 89 centers, an average of 2.3 CVT patients were seen at each participating center in a given year.[2] Population-based figures are lacking, but indirect estimates from autopsy data as well as large clinical series suggest 3 to 4 cases per million population, with the majority of patients (75%) being women.[3] As with other intracranial disorders, our mechanistic understanding of this condition has been greatly enhanced in the modern era, as imaging techniques (especially magnetic resonance venography and angiography) have helped revise previous assumptions. The pathophysiology, clinical spectrum, and diagnostic approach for CVT have been discussed elsewhere in this issue. This review focuses on the role of heparin in the management of CVT patients.

Clinical considerations

Clinical presentation of CVT is notoriously variable, making a high index of clinical suspicion mandatory. Neurological manifestations are produced by focal effects of venous obstruction, including oedema, infarction and local haemorrhage, as well as by raised intracranial pressure.[4] Most patients, therefore, present with headache, with or without focal deficits. In 10-30% cases an encephalopathic presentation may dominate, which can be clinically misleading. An identifiable cause or predisposing condition is found in over 80% of cases.[4] The list of possible causes is long, but they can generally be grouped into infectious (e.g., otitis or mastoiditis), mechanical (e.g., trauma or neurosurgical procedure), and medical (e.g., hypercoagulable states or inflammatory bowel disease) etiologies. Prognosis is generally favourable. In a recent large prospective series of 624 cases, 80% of patients recovered to a modified Rankin score of 0 or 1 (functional independence); 8% of patients died, 7% had mild impairments, and 5% remained moderately to severely disabled.[2] Thus with accurate diagnosis and prompt therapy, majority of patients are able to approach prior levels of functioning.

An established diagnosis is a prerequisite for treatment. The goal of treatment is to arrest clot propagation; therefore, diagnosis must be urgently established and therapy begun expeditiously. Because of the variable symptomatology, diagnosis may be delayed unless suspected early and frequently. The investigation of choice is MRI of the brain with standard sequences (T1, T2, FLAIR), plus cranial MR venography.[5]

Treatment is aimed at general measures to relieve raised intracranial pressure, as well as specific measures targeting the thrombotic process. Unlike in arterial thrombosis, where clot formation depends on atherosclerotic plaque inflammation and platelet activity, venous thrombosis results from activation of the coagulation cascade. Anticoagulant and anti-thrombotic strategies are therefore the cornerstone, and there is no pathophysiologic rationale for the use of anti-platelet agents in CVT.[4] Although endovascular thrombolysis has been increasingly used, anticoagulation with heparin remains the time-honoured treatment. Studies are needed to establish the advantage, if any, of endovascular thrombolysis over heparin, and especially to identify subsets of patients who may be best treated with thrombolytic therapy.[3] Evidence favouring the use of heparin is largely circumstantial, and an adequately powered high-quality randomized clinical trial testing the efficacy of heparin against placebo in CVT is still awaited. Nevertheless, based on available data, the therapy continues to be the mainstay of CVT management.

Pharmacology of heparin

Heparin has been in clinical use for 60 years [6]. It is a polysaccharide mixture comprising glycosaminoglycans of varying molecular size that incorporate a unique pentasaccharide structure binding to and inhibiting anti-thrombin III. With intravenous administration, anticoagulant effect is rapidly achieved. Dosing is variable, and must be adjusted to maintain the activated partial thromboplastin time (aPTT) prolonged at 1.5 to 2.0 times the normal laboratory control. A typical starting regimen is 5,000 units given by IV bolus, followed by a continuous infusion of 1,000 units per hour, with subsequent adjustment according to periodic and careful aPTT measurement. Weight-adjusted doses and dosing nomograms have also been developed.[6] Subcutaneous injection of heparin may also be used, but higher doses are required. Intravenous administration is the preferred method, however, as the subcutaneous route is associated with unreliable bioavailability and delayed onset of anticoagulant effects.

Low molecular weight heparin (LMWH) is a more recent version of heparin that has been available over the last 20 years. It was developed to minimize the bleeding complications associated with unfractionated (standard) heparin. LMWH is prepared by depolymerizing heparin into lower molecular weight fragments that are approximately one-third the size of standard heparin. There are clear advantages in terms of more reliable dose-response pharmacokinetics, and a reduced propensity for the platelet inhibition seen with standard heparin (heparin-induced thrombocytopenia or HIT).[7] Because of a more predictable anticoagulant response, laboratory coagulation monitoring is not needed. Based on uncontrolled as well as placebo-controlled evidence, LMWH is effective in the management of CVT and can be used as an alternative to unfractionated heparin.[8] However, there has yet to be a study that provides a head-to-head comparison of LMWH with unfractionated heparin in this setting.

Evidence of efficacy

Over the years, the use of heparin in CVT has been supported by case reports as well as retrospective and prospective uncontrolled series.[9-11] To date, three randomized placebo-controlled trials have also examined the efficacy of heparin in CVT.[3] However, the numbers of patients are small and there have been methodological limitations. As the demand for quality medical evidence becomes more stringent, the absence of an adequately powered clinical trial addressing this question in a definitive fashion is acutely felt.

Einhaupl and colleagues[10] reported a randomized double-blind trial of 20 patients (10 heparin, 10 placebo) from Germany in which outcome was assessed by a freshly-formulated clinical scale of CVT severity. At 3-month follow-up, 8 of 10 patients in the heparin group had completely recovered, compared with only 1 of 10 in the placebo group ($p < 0.01$). Although there was no mortality in the heparin group, 3 patients died in the placebo group. In a study from Amsterdam, de Bruijn and Stam.[8] randomized 60 patients to receive either nardoparin (a low-molecular-weight heparin) or placebo, and found a greater likelihood of favourable outcome from nardoparin; however, the difference between the two groups was not statistically significant. A third trial reported results of 57 women with peripartum CVT randomized to heparin or placebo in India.[12] There was a non-significant benefit favouring heparin, but the result has limited interpretation as CVT diagnosis in this study was not confirmed by MRI. A pooled analysis of the German and Dutch trials concluded that anticoagulant treatment of CVT is safe and produces a "potentially important" reduction in the risk of death or dependency which, however, does not reach statistical significance.[13] Additional trials are needed to definitively establish the benefit of heparin in CVT with statistical significance. It has been estimated that an adequately powered trial that anticipates the previously observed effect size would need to recruit 300 patients.[3]

An important conclusion from the available data on heparin use in CVT is regarding safety. The frequent presence of oedema and especially haemorrhagic venous infarction has been a deterrent for many clinicians fearing aggravated intracranial bleeding; indeed, the issue has historically been somewhat controversial.[4] Observations from uncontrolled series of heparin-treated CVT patients confirm that (assuming vigilant monitoring of the aPTT) the risk of aggravated intracranial bleeding is minimal to none, and even the presence of haemorrhagic infarction is not a contraindication to treatment.[3,4] The trial by de Bruijn and Stam[8] for example, included 25 patients with haemorrhagic infarction who received heparin without adverse effects. It is now considered standard practice to continue heparin in the acute phase, followed by oral anticoagulation with warfarin. Heparin is administered regardless of the etiology of the thrombosis and is only withheld in case of a general medical contraindication to heparin such as hypersensitivity. The optimal duration of treatment with either heparin or oral anticoagulation remains unclear. Most neurologists (including our own group) will administer heparin for the first few days followed by anticoagulation with warfarin for 3-6 months with a target international normalized ratio (INR) of 2.5.

Limitations and prospects

Anticoagulation is a potentially difficult therapy with side-effects that can limit its use. Although the risk of bleeding complications is minimized with rigorous monitoring and control of the aPTT, the burden of laboratory monitoring is nevertheless costly and cumbersome. In up to 3% cases, heparin use is also associated with an immune-mediated thrombocytopenia (heparin-induced thrombocytopenia or HIT)[6]; the condition is characterized by IgG-mediated platelet activation and paradoxically creates a prothrombotic state. Treatment is challenging and may require use of ancrod, a defibrogenating agent prepared from snake venom. Rarely, hypersensitivity reactions to heparin are also seen. Novel anti-thrombotic agents are emerging that may circumvent the limitations of traditional anticoagulants such as heparin and warfarin.[14] Lepriudin and argatroban are direct thrombin inhibitors that appear to have efficacy in patients developing heparin-induced thrombocytopenia. Ximelagatran is also a direct thrombin inhibitor that has demonstrated safety and efficacy in the management of venous thromboembolism; it appears likely it will benefit CVT patients and should be examined in a Phase III clinical trial.

References

1. Ribes MF. Des recherches faites sur la phlebite. Revue Medicale Francaise et Etrangere et Journal de Clinique de l'Hotel-Dieu et de la Charite de Paris 1825; 3:5
2. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004; 35:664-70.
3. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005; 352:1791-8.
4. Bousser MG, Barnett HJM. Cerebral venous thrombosis. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM (eds.) Stroke: Pathophysiology, Diagnosis and Management, Churchill Livingstone (New York); 1998:623-7.
5. Lafitte F, Boukobza M, Guichard JP, Hoeffel C, Reizine D, Ille O, Woimant F, Merland JJ. MRI and MRA for diagnosis and follow-up of cerebral venous thrombosis (CVT). Clin Radoil 1997; 52:672-9.
6. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119(1 Suppl):64S-94S.
7. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337:688-98.
8. deBruijn SF, Stam J. Randomized placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke 1999; 30:484-8.
9. Bousser MG, Chiras J, Bories J, Castaigne P. Cerebral venous thrombosis: a review of 38 cases. Stroke 1985; 16:199-213.
10. Einhaupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, Haberl RL, Pfister HW, Schmiedek P. Heparin treatment in sinus venous thrombosis. Lancet 1991; 338:597-600.
11. Halpern JP, Morris JGL, Driscoll GL. Anticoagulants and cerebral venous thrombosis. Aust NZ J Med 1984; 14:643-8.
12. Nagaraja D, Rao BSS, Taly AB, Subhash MN. Randomizd controlled trial of heparin in puerperal cerebral venous/sinus thrombosis. Nimhans J 1995;13:111-5.
13. Stam J, deBruin SF, deVeber G. Anticoagulation for cerebal sinus thrombosis. Stroke 2003; 34:1054-5.
14. Franvis CW. Direct thrombin inhibitors for treatment of heparin induced