Cerebral Venous Thrombosis
Another Heparin Controversy
Magdy Selim, MD, PhD

See related article, p 298.

Results from clinical studies and advances in radiological diagnosis during the past 20 years have significantly altered the management of patients with cerebral venous thrombosis (CVT), with resultant improvement in overall prognosis and decreased mortality. Although the efficacy of anticoagulation in CVT has not been unequivocally proven, it is widely used as the mainstay therapy. There is a pathophysiological rationale to recommend the use of anticoagulation in CVT. Occlusion of cerebral venous system impairs blood outflow from the brain, resulting in increased intracranial and capillary pressure and subsequently intracerebral hemorrhage (ICH). The use of anticoagulation can theoretically prevent thrombus propagation, facilitate recanalization of the occluded venous sinus, and improve venous outflow.

Scattered case reports and series in the literature described the successful use of heparin in CVT since the 1940s.1,2 In the early 1990s, Einhäupl et al3 performed the first randomized controlled study: 20 patients with CVT were randomized to a placebo versus heparin. Patients treated with heparin showed significant improvement; all of the heparin-treated patients survived, and 80% had a complete clinical recovery after 3 months. No new cases of ICH occurred after initiation of heparin. Einhäupl et al also reported their retrospective experience in 43 patients with CVT with ICH; 27 patients were treated with intravenous heparin after the ICH. Of these, 15% of patients died compared with 69% of patients who did not receive heparin, and 52% of patients completely recovered. The authors concluded that anticoagulation is an effective treatment in patients with CVT, and that ICH is not a contraindication to anticoagulation. De Bruijn and Stam4 followed up by a larger randomized double-blinded placebo-controlled multicenter trial; 30 patients were randomized to subcutaneous nadroparin (180 U/kg per 24 hours), and 29 patients were treated with intravenous heparin after the ICH. Of these, 15% of patients died compared with 69% of patients who did not receive heparin, and 52% of patients completely recovered. The authors concluded that anticoagulation is an effective treatment in patients with CVT, and that ICH is not a contraindication to anticoagulation. De Bruijn and Stam also reported their retrospective experience in 43 patients with CVT with ICH; 27 patients were treated with intravenous heparin after the ICH. Of these, 15% of patients died compared with 69% of patients who did not receive heparin, and 52% of patients completely recovered. The authors concluded that anticoagulation is an effective treatment in patients with CVT, and that ICH is not a contraindication to anticoagulation. De Bruijn and Stam also reported their retrospective experience in 43 patients with CVT with ICH; 27 patients were treated with intravenous heparin after the ICH. Of these, 15% of patients died compared with 69% of patients who did not receive heparin, and 52% of patients completely recovered. The authors concluded that anticoagulation is an effective treatment in patients with CVT, and that ICH is not a contraindication to anticoagulation.

A Cochrane review,5,6 using these 2 trials for meta-analysis, found that anticoagulant therapy was associated with a pooled relative risk of death of 0.33 (95% confidence interval, 0.08–1.21) and of death or dependency of 0.46 (95% confidence interval, 0.16–1.31). The absolute reduction in the risk of death or dependency was 13% (95% confidence interval, 30% to ~3%). The Cochrane investigators concluded that anticoagulant treatment for CVT seems to be safe even in patients with ICH. They acknowledged that the reduction in the risk of death or dependency did not reach statistical significance, and that clinicians will need to base their treatment decisions on the limited evidence available. A retrospective review by the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)7 also showed a nonsignificant but definite trend toward improvement with anticoagulation. A recent single-center prospective study of 162 neonates and children with CVT found that although major hemorrhages occurred in 6% of patients treated with anticoagulation, they were all nonfatal, and clinical outcome was favorable in 50% of patients. Anticoagulation significantly reduced thrombus propagation, which was associated with new venous infarcts and worse clinical outcome. The authors concluded that anticoagulation merits strong consideration in pediatric CVT. The latest American Heart Association/American Stroke Association and European Federation of Neurological Societies guidelines, which are based largely on the ISCVT, recommend that anticoagulation should be given to all patients with CVT who do not have contraindications for anticoagulation.8,9 Based on the above trials and professional guidelines, anticoagulation continues to be the standard of care for nearly all patients with CVT.

However, in the absence of large-scale randomized trials and statistical significance, it is not surprising to find skeptics with descending opinions that anticoagulation cannot be recommended for all patients with CVT. In this issue of Stroke, Dr David Cundiff reviews all published reports from 1990 to 2013 about the safety and efficacy of anticoagulation in patients ≥15 years of age with CVT (62 studies, including 5155 patients), thereby including a large number of studies that were excluded from the Cochrane review. He reports that the risk of venous thrombosis recurrence was significantly higher while patients took anticoagulants, and that the risk of harm from anticoagulants, particularly from bleeding, was...
considerable. He argues that anticoagulation for CVT is not evidence based to be effective or safe.

The study by Cundiff has several limitations that significantly limit the interpretation of his findings and conclusions. Despite the author’s reliance on personal communications to obtain unpublished data on outcome and anticoagulation status from previously published studies, only a handful of studies provided part or all of the data. Similarly, few studies reported data on the recurrence of venous thrombosis. In addition, calculating the rate of recurrence per month is less than ideal given that the follow-up duration in various studies varied from <3 months to >3 years. In addition, the impact of selection bias on the choice of therapy in various patients cannot be either ascertained or ignored. Finally, there are several missing important data elements from Cundiff’s study, such as the cause and risk factors for death in anticoagulated patients (Table 2); one needs to know to ascertain that their death was related to anticoagulation.

Despite these limitations, Cundiff indeed raises valid concerns and questions of clinical and therapeutic importance that are yet to be fully answered. The use of anticoagulants in patients with CVT poses a real risk: ICH. There is paucity of data about the de novo occurrence or worsening of ICH after anticoagulant treatment in a larger number of patients to obtain more robust estimation of the risk. Similarly, reliable data about the subgroups of patients with CVT who may or may not benefit from anticoagulation therapy are lacking. Should the extent, number, and location of the affected sinuses and the identified cause(s) for CVT influence the decision-making?

Perhaps the most intriguing aspects of Cundiff’s review are his findings that in-hospital death rate was lower in anticoagulated patients (9% versus 14%; Table 1), and that patients receiving posthospitalization anticoagulants had lower death rates (1.6% versus 6.9%; Table 4); that is, anticoagulation decreases mortality.

Therefore, the question becomes whether anticoagulants should be avoided in the name of safety in the absence of large-scale randomized trials and statistical significance. Are you willing to embark on a new trial that includes a placebo group? Is there a role for newer anticoagulants in CVT? What about antiplatelet therapy? Needless to say, the existing evidence-based guidelines for management of CVT would benefit from more evidence.

Disclosures
None.

References

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