Cerebral Venous Thrombosis
Nothing, Heparin, or Local Thrombolysis?

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Two articles in this issue of Stroke\textsuperscript{1,2} draw our attention to cerebral venous thrombosis (CVT), an infrequent but fascinating condition, remarkable for its extreme diversity, which still makes it a diagnostic and therapeutic challenge. Headache, focal deficits, seizures, disorders of consciousness, and papilledema, which can present in isolation or in association, are the most frequent signs.\textsuperscript{3} The mode of onset is highly variable, anything from sudden to progressive over weeks, so that CVT can mimic a host of conditions, such as ischemic or hemorrhagic stroke, abscess, tumor, encephalitis, metabolic encephalopathy, benign intracranial hypertension. . . .

Given this amazingly diverse clinical presentation, CVT should be considered in almost any brain syndrome, and appropriate neuroimaging investigations should be performed whenever suspicion is raised. A CT scan is usually the first investigation performed on an emergency basis. Although it can sometimes detect the spontaneously hyperdense thrombosed sinus, it usually shows nonspecific changes such as hypodensities, hyperdensities, and contrast enhancement, and in up to 30\% of cases it is normal.\textsuperscript{3,4} The present "gold standard" for the diagnosis of CVT is no longer angiography but MRI, which visualizes the thrombosed sinus as an increased signal on both T1- and T2-weighted imaging. MR angiography or helical CT venography are nevertheless indicated at very early (before day 5) or late (after 6 weeks) stages when false-negatives may occur, or whenever MRI shows equivocal signs.

Once CVT is recognized, the next step is to find its etiology from among the over 100 causes that have been identified, which schematically encompass all causes of deep-vein leg thrombosis and numerous local causes such as traumas, tumors, or infections.\textsuperscript{3} However, despite an extensive initial work-up, the proportion of cases of unknown etiology remains between 20\% and 25\%.\textsuperscript{3,4} This stresses the need, when no cause is found, for a prolonged follow-up with repeated investigations.

One of the most puzzling aspects of CVT is its diversity in outcome. Recognized as early as 150 years ago, CVT has for a century been diagnosed almost exclusively at autopsy and therefore thought to be always lethal. In early angiographic series, mortality still ranged between 30\% and 50\%, but in a number of recent series\textsuperscript{4,5} it was \(\leq 10\%\). Many factors of bad prognosis have been identified, including extreme age, coma, involvement of cerebellar veins or of the deep venous system, severely raised intracranial pressure, infectious or malignant etiologies, hemorrhagic infarcts on CT scan, and intercurrent complications such as uncontrolled seizures or pulmonary embolism.\textsuperscript{3–8} However, although it is by far much better than that of arterial stroke, the outcome of CVT remains largely unpredictable. It is not unusual to see deeply comatose or severely hemiplegic patients recover dramatically, without any sequelae.\textsuperscript{3} Conversely, a patient with headache as the only presenting symptom can suddenly worsen, with a dense hemiplegia if thrombosis spreads from a sinus to a cerebral vein. Interestingly, it is well established that clinical recovery starts much more rapidly than vessel recanalization and can occur even in the absence of recanalization.\textsuperscript{3,7,9}

CVT is thus an infrequent condition that is extremely variable in its clinical presentation, mode of onset, imaging appearance, and outcome, which often occurs in a nonneurological setting. Its prognosis, although much better than classically thought, remains largely unpredictable, with a wide discrepancy between clinical recovery and vessel recanalization. It is thus not surprising that neurologists—many of whom have little experience with this condition—have not reached a consensus about treatment, particularly regarding the use of antithrombotic drugs.

First advocated over 50 years ago,\textsuperscript{10} heparin has been more and more widely used as evidence has accumulated that it is both effective and safe, even in hemorrhagic lesions.\textsuperscript{3,4,7–9} Its effectiveness was suspected because of the dramatic improvement observed in some cases immediately after the initiation of heparin and the good prognosis of heparin-treated patients in a large retrospective and prospective series.\textsuperscript{4,7–9} It was confirmed by the results of the first randomized trial,\textsuperscript{11} which compared dose-adjusted intravenous heparin and placebo, and which was stopped after 20 patients because of the dramatic difference observed between the 2 groups: 8 patients in the heparin group but only 1 in the placebo group recovered fully. There were no deaths in the heparin group; in contrast, there were 3 in the placebo group.

The results of this German trial were challenged,\textsuperscript{12} however, controversy persisted,\textsuperscript{13} and a new—mostly Dutch—trial was performed that is reported in this issue.\textsuperscript{3} From 1992 to 1996, 60 patients were randomized between low-molecular-weight heparin (LMWH) (subcutaneous nadroparin, 90 anti-Xa units/kg twice daily) and matching placebo for 3 weeks. After this double-blind part of the study, the code was broken and patients allocated nadroparin received oral...
anticogulants (INR, 2.5 to 3.5) for 10 weeks. There were no major differences between the 2 groups at entry, except for isolated intracranial hypertension (ICH), which occurred twice as frequently in the placebo group as in the nadroparin group. This imbalance should not be neglected, since CVT patients with isolated ICH have a much better prognosis than those with seizures, focal deficits, or coma. A poor outcome, defined as death or Barthel Index score of <15, was observed at 3 weeks in 6 of 30 nadroparin-treated patients (20%) and 7 of 29 control subjects (24%) and observed at 12 weeks in 13% and 21%, respectively. This corresponds to an absolute risk reduction of 7% and a relative risk reduction of 38%. A complete recovery was observed in 20% of anticoagulated patients and 28% of controls. None of these differences was statistically significant. No worsening attributable to new or enlarged cerebral hemorrhage was observed in anticoagulated patients, even among the 15 who had hemorrhagic lesions demonstrated on CT scan.

This study confirms some important facts about CVT but again raises questions about the efficacy of heparin. Points that are confirmed include a lower mortality (10%) than historically thought, the possibility of a full recovery without antithrombotic treatment, the more severe prognosis of CVT with hemorrhage (6 deaths) than without (no deaths), and the safety of heparin, even in patients with hemorrhagic lesions on CT.

The negative results obtained in the present trial contrast sharply with the major benefit of heparin observed in the German trial. The reasons for this discrepancy are unknown. Given the small number of poor outcomes in the Dutch trial, it could be that the imbalance observed regarding the number of patients with isolated ICH has favored the placebo group, but not to the point of explaining such a discrepancy. Patients in the Dutch trial were treated earlier (10 days) than those in the German trial (30 days) and their conditions were less severe, with a mortality of 13.8% versus 30%, but again, it is difficult to understand how this could explain a major difference in the efficacy of heparin. Treatment modalities were not the same in the 2 trials: dose-adjusted intravenous unfractionated heparin in the German trial, body weight–adjusted subcutaneous LMWH in the Dutch trial. LMWH has recently been shown to be at least as safe and effective as unfractionated heparin in the treatment of deep venous thrombosis (DVT) and hemodynamically stable pulmonary embolism, and “the end of the heparin pump” has even been predicted. It is therefore unlikely that this difference in modalities of heparin administration explains such differences in efficacy. Nevertheless, if one considers that results of DVT trials apply strictly to CVT, then one could question the need and even the ethics of placebo-controlled trials in this condition. One must thus admit that in CVT, there is still some uncertainty as to the relative efficacy of intravenous heparin and LMWH.

The authors of the European trial have performed a meta-analysis of the 2 available trials which shows that with heparin there is an absolute risk reduction in mortality of 14% and in death or dependency of 15%, with relative risk reductions of 70% and 56%, respectively. Again, numbers are small, confidence intervals are wide, and these differences do not quite reach statistical significance. They are, nevertheless, highly meaningful from a clinical standpoint, and taken together with the safety of heparin and the unpredictability of the outcome, they reinforce the use of heparin as first-line treatment of CVT.

This view is now challenged by the advocates of direct endovascular thrombolytic therapy, as performed in the study by Frey et al and reported in this issue.

Vines and Davis in 1971 were the first to report on the use of urokinase in CVT, followed 10 years later by Di Rocco et al, who successfully treated 5 patients with intravenous urokinase and heparin. In 1988 Scott et al reported the first case of local fibrinolytic therapy in a young patient with an extensive superior sagittal sinus (SSS) thrombosis. A local urokinase infusion was performed via a frontal burr hole, and the patient, who was initially decerebrate, made a good recovery despite the occurrence of an hemorrhagic infarct. In the following years, some 30 cases have been reported of local infusion of urokinase (at doses ranging from 470 000 to 13.79 million units) achieved by the internal jugular or, more frequently, the femoral route. The largest series is that of Horowitz et al, who treated 13 patients with extensive thrombosis of several sinuses (SSS in 12, lateral sinus in 12, and straight sinus in 4). Sinus patency and good recovery were obtained in 12 patients. There was no worsening, despite the presence of a hemorrhagic infarct in 4 patients.

More recently, recombinant tissue plasminogen activator (rtPA) has been used (in combination with heparin) because of its many theoretical advantages, which might help to decrease the hemorrhagic risk: it is clot selective, it has a short half-life of 7 to 8 minutes, it avoids plasminemia, and it produces the lowest level of fibrinogen degradation products. The American series of 12 patients reported in this issue is the largest so far, and taken together with the only other reported series (Kim and Suh, with 9 patients), it brings some very useful information: complete flow restoration was obtained in a majority of cases (6 of 12 in the present American study, 9 of 9 in the series of Kim and Suh), together with a complete recovery in many cases (5 of 12 and 9 of 9, respectively). Flow restoration was rapid: on average, 29 and 18 hours, respectively. Although no such precise data are available for heparin, it is obvious that complete recanalization is more frequent and faster with rtPA plus heparin than with heparin alone, and it is also faster than with urokinase (an average of 71 hours for 29 reported patients). It is interesting to note that recanalization can be obtained even in patients treated long after the onset of symptoms, up to 16 weeks in 1 case. However, the correlation between flow restoration and clinical recovery, although good, was far from perfect: 1 patient improved despite the absence of flow restoration, and 2 patients recovered completely despite incomplete flow restoration; in contrast, 1 patient had flow restoration but recovered incompletely. Other parameters, such as collateral circulation, are thus bound to play a crucial role in clinical recovery, which, in the end, is clearly the single most pertinent outcome criteria.

Local rtPA carries an indisputable risk. In the Korean study, there were 2 complications: a minor bleeding at the femoral puncture site and a major intrapelvic hemorrhage that required surgery in 1 case. In the 2 studies, a total of 7
subjects had hemorrhagic lesions before treatment; 2 of these deteriorated because of hemorrhagic worsening. This contrasts with the absence of deterioration in the 15 patients with hemorrhagic lesions treated with heparin in the Dutch trial.1

Local rtPA therefore carries a higher risk of intracerebral hemorrhage than heparin alone in patients with a previous hemorrhagic lesion. In patients without pretreatment hemorrhage, local rtPA appears safe, but the numbers are very small compared with those of heparin-treated patients. The methods of rtPA administration (repeated bolus or bolus plus infusion) and the optimal dosage remain to be determined: a much lower mean dose was used in the American study (46 mg; range, 23 to 128 mg) than in the Korean study (134 mg; range, 50 to 300 mg), although there was no obvious difference in the type and number of sinuses involved.

Thus, although more and more patients with CVT are treated by local endovascular urokinase or rtPA, it is still extremely difficult to precisely assess the benefit-to-risk ratio of this treatment. From what is reported, local thrombolysis appears to restore flow more frequently and rapidly than heparin alone; however, first, there is no evidence that the clinical outcome is better, and second, the hemorrhagic risk is greater, at least when there is already a pretreatment hemorrhage. Therefore, there is at present no good scientific evidence to recommend local thrombolysis as the first-line treatment for CVT. Furthermore, this treatment would not be feasible in many poor countries where CVT is particularly frequent. The question of local thrombolysis, then, arises only if the condition of the patient worsens despite heparin and symptomatic treatment, provided other causes of worsening—such as uncontrolled seizures, concomitant pulmonary embolism, or aggravation of a severe underlying condition—have been excluded. The most frequent cause of worsening, however, is inadequate anticoagulation, and in our experience and that of others, it is extremely rare to observe a deterioration of clinical course due to progression of thrombosis in properly anticoagulated patients.5,4,7,9,11 Should this occur, local thrombolysis would be indicated.3,23

In conclusion, the 2 articles on CVT in this issue help to clarify our attitude toward treatment. The new randomized trial of heparin1 has shown once again that heparin is safe and the benefit, although statistically not significant, is clinically relevant, particularly when combined with the results of the previous randomized trial. This indicates that as long as we are unable to predict which CVT patient will recover spontaneously, first, heparin is indicated whatever the clinical or neuroimaging pattern, and second, no placebo group should be included in further randomized trials. The open series of 12 patients treated with intrathrombus rtPA associated with intravenous heparin2 has demonstrated that recanalization is faster and more frequent but without evidence of a better clinical outcome and at the expense of an increased hemorrhagic risk, at least in patients with pretreatment hemorrhagic lesions. Given the frequency of a good outcome with heparin and the large number of patients that would be required,1 a randomized trial of heparin alone versus local thrombolysis plus heparin is not the priority. It seems more urgent to concentrate our efforts on early diagnosis and optimal treatment and on the establishment of an improved risk stratification that would perhaps allow us to treat some of our CVT patients with heparin, others with thrombolysis, and possibly some with nothing. This time has not yet come, and in 1999 heparin remains the first-line treatment for CVT because of its efficacy, safety, and feasibility. The adjudication of local thrombolysis is indicated in the rare cases of worsening despite adequate anticoagulation and optimal symptomatic and etiologic treatments.

References


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