Cerebral venous thrombosis: anticoagulants or thrombolytic therapy?

After Ribes’ initial description in 1825 of a patient with cerebral venous thrombosis (CVT), this disorder was universally considered to be fatal, the diagnosis being made at postmortem. In the past 3 decades, as a result of the development and increasing availability of non-invasive neuroimaging techniques, CVT is increasingly recognised, not just in the neurology or neurosurgery wards but now in acute medical receiving and stroke units. It is difficult to estimate the incidence of CVT in the absence of epidemiological studies. Early postmortem studies showed a low incidence, 21.7 persons/year in England and Wales between 1952 and 1961, whereas recent clinical series suggest that the incidence is possibly 10 times higher.2 3 It is evident that clinical presentation, imaging appearances, causation, and outcome of this disorder (or group of disorders) are variable, emphasising its heterogeneity. With such clinical diversity and absence of large adequately powered designed clinical trials, the optimum treatment remains uncertain, in particular the appropriate place of supportive treatment alone, anticoagulants, or endovascular thrombolysis. Bousser4 in an excellent editorial, accompanying two recent articles on treatment,5 6 drew attention to the dilemma of “nothing, heparin or local thrombolysis”. This overview stressed the extreme diversity of CVT and concluded that “heparin remains the first-line treatment for CVT because of its efficacy, safety and feasibility”. Despite the lack of definitive supporting evidence, placebo controlled or comparative studies of heparin with thrombolysis were not regarded as priorities. This editorial importantly stressed the need to stratify risk within the patient population but its conclusions on management did not seem to clarify matters for the stroke physician or neurologist, increasingly confronted with how to best manage this disorder. An earlier survey of 13 teaching hospitals in The Netherlands disclosed eight centres opposed to the use of anticoagulants in CVT and five in favour.7 In a recent postal survey of all the members of the Association of British Neurologists, 120 consultant neurologists replied, of whom 67.5% considered that there is no standard treatment for CVT and 97.5% thought that further studies were needed. There was divided opinion among the neurologists as to what type of heparin to use, 19% in favour of using unfractionated, 18% of low molecular weight, and 70% with no preferences. When they asked about endovascular thrombolysis, 60% considered it as a treatment choice in extreme circumstances. This survey shows the current lack of clarity among British neurologists as to how this condition should be best managed.

The aim of this editorial is to assess the evidence of safety and efficacy for anticoagulants or endovascular thrombolysis in patients with CVT in comparison with natural history/placebo. The literature was searched, using Medline, Cochrane library, and hand searches of published reference lists, for studies or case reports of heparin and/or endovascular thrombolysis as a treatment for CVT. The present knowledge of the nature, history, and treatments are discussed with their supportive evidence. Areas of uncertainty and the need for further studies are emphasised.

Outcome and natural history of CVT

Recent retrospective series show that most patients with CVT have a favourable outcome with mortality varying between 5% and 30%.5 7 8 11 The main causes of death are haemorrhagic infarction with raised intracranial pressure or complications such as brain herniation with cerebral oedema, status epilepticus, sepsis, pulmonary embolism, or the severity of an underlying causal systemic disorder such as malignancy.7 Although individual outcome is generally unpredictable, those who present with headache and papilloedema alone have a good prognosis.10 In comparing the outcome of 67 patients with CVT related to pregnancy and puerperium with 46 due to other causes, 80% compared with 58% had good outcome indicating that underlying causation is an important prognostic factor, obstetric patients doing best.7 Cautu and Barinagarrementeria suggested that “a more limited and transient occlusion, with rapid sinovenous recanalisation by spontaneous thrombolysis or development of collaterals” is the reason for the benign outcome of CVT in obstetric cases. For other causes, there is insufficient evidence on the effect of congenital thrombophilias on outcome. Raizer and DeAngelis12 reviewed CVT occurring in patients with cancer and concluded that, “with or without anticoagulation, most patients make an excellent recovery”. Generally, however, there is uncertainty about the effect of the underlying cause, when defined, in predicting natural history and outcome.

Clinical features signifying a poor prognosis are rapidity of onset, early reduced Glasgow coma score (GCS), focal neurological signs, seizures, and concomitant infection.13 In one series, all six patients presenting with coma were treated supportive and died as a result of the thrombosis.14 A further study of 110 patients showed that
six died acutely, two shortly thereafter, and 25 were lost to follow up. The remaining patients were followed up for a mean period of 6.5 years during which time 85% had no neurological sequelae.11 Sixty-two of these patients had been given “heparin for a few days followed by oral anticoagulation for 3 to 4 months”. In another sizeable study of 38 patients with CVT, four died and seven were left with neurological sequelae, 84% of these patients were treated with heparin.12 The data on the natural history of CVT are based in retrospective studies and case reports containing heterogeneous patient groups and thus is misleading. The only prospective data available were from the placebo arms of the heparin studies, which showed a poor outcome in up of 45% of patients,13 being much greater than those from retrospective studies. This may indicate a selection bias for such studies.14 Study design and different methods of assessing outcome may well explain this variable literature.

In the postal survey of British neurologists, 87% thought that the natural history of untreated CVT is unknown and that there is the need for further studies to consider this.

Heparin as a treatment of CVT
Heparin as a treatment for CVT was advocated by Martin and Sheehan 60 years ago15 and is considered by many still to be the standard therapy.16 Antithrombotic agents may limit the spread of thrombus and promote its dissolution. Low molecular weight heparin or heparinoids when compared with unfractionated heparin have a longer half life, predictable response to fixed dosing, and a lower incidence of thrombocytopenia and haemorrhagic complications. There are only two randomised controlled trials of heparin. Einhäupl et al16 randomised 20 patients to intravenous unfractionated heparin (bolus dose of 3000 IU and continuous infusion of 25 000–65 000 IU/day), or placebo (intravenous continuous saline infusion). The patients were blinded to the treatment though not the treating physician. Clinical outcome was assessed daily by a blinded assessing physician using a specifically developed “sinus venous thrombosis severity scale” graded 1–9 in which 1 represent minimal symptoms and signs, and 9 represents death. They reported complete recovery in eight out 10 patients in the heparin group, the remaining two having minor neurological deficit. One patient in the control group made a complete recovery, six patients had a neurological deficit, and three patients died. A retrospective cohort of 102 patients was incorporated into the study to assess the safety of heparin; in 27 with intracranial haemorrhage receiving heparin, four died and two had severe neurological deficit whereas nine of 13 patients not receiving heparin died. On the basis of the two components of this study the authors concluded that heparin is effective and the CT presence of haemorrhagic venous infarction is not a contraindication for its use. Although this study provides some support for the use of intravenous unfractionated heparin, some authors have challenged the methods used in outcome assessment, mainly the use of the unvalidated “sinus venous thrombosis severity scale”. Stam et al17 noted that the statistical significance between the two groups was based on six patients in the control with residual neurological deficit, but with closer scrutiny of these patients’ outcome, five had transient focal signs and one had mild paresis and if they are regarded as having recovered, the trial would not show significant treatment effect; Stam et al thus regarded the study as inconclusive.

There was also a significant delay before treatment was instigated (a mean of 33 days in the heparin group and 25 days in the placebo group), unlike an acute “real life” situation. Finally, this study failed to clarify the issues of duration of heparin treatment and the utilisation of warfarin.

Curiously, as noted in a previous editorial18 the study was completed in 1984, but published in 1991.

De Bruijn et al19 reported a randomised, placebo controlled trial of low molecular weight heparin (Nadroparin) in 60 patients with CVT, followed by an open arm of 10 weeks of warfarin in those allocated to heparin. They used the Barthel index of activities of daily living assessed at day 21 as the primary end point and Oxford handicap scale and Barthel index at 12 weeks to assess the long term outcome; 20% of patients in the treatment group and 24% in the placebo group had a poor outcome after 3 weeks, and 13% in the treatment and 21% in the placebo group a poor outcome at 12 weeks. There was no statistically significant evidence of a treatment effect between the two groups.

A meta-analysis of the these studies showed no significant effect of heparin in CVT.20 However, the combined risk of “death or dependence” was ~15% in the anticoagulated group and the authors therefore concluded that heparin has modest but “clinically important” benefit on CSVT. It is clear that there were few similarities between the two trials, having used different outcome measures and heparin types, rendering their synthesis in a meta-analysis probably unsound. Even if the results of this meta-analysis were to be accepted it still shows no benefit of heparin over placebo.

In both of these studies new symptomatic cerebral haemorrhages were not encountered, indicating that heparin seems safe. None the less, this cannot be stated with absolute certainty as the times from treatment and administration of heparin in the intravenous heparin study, Brucker et al19 reported a retrospective review of 42 cases of CVT treated with intravenous heparin followed by oral anticoagulant.

Only one of these patients died and another was left with severe neurological disability; 26 patients made a complete recovery and 14 had mild neurological deficit. No enlargement of pre-existing haemorrhagic transformation was reported on the follow up CT in 22 patients showing this on initial imaging. This study would seem to support the safety of using heparin; however, it did not contribute further evidence on the efficacy due to the absence of control group.

These studies do not produce conclusive evidence and indicate the need for larger trials to establish the role of heparin before unequivocally accepting that it is the standard treatment for all CVT, although some would argue that the evidence of safety alone is a justification for its use. Issues in relation to the type of heparin and the need and duration of oral anticoagulant (often dictated by presence of underlying disease) need further clarification (for summary of heparin studies, refer to table 1).

Endovascular thrombolysis in CVT
Randomised controlled trials of endovascular thrombolysis in CVT are lacking, its utilisation being based on observations reported in uncontrolled case series. Favourable outcome with no major therapeutic morbidity has been described in series where the majority received urokinase.13 14 20–24 Within these was substantial variability in the clinical severity of CVT, the dose of thrombolytic agent given, duration of treatment, and concomitant use of anticoagulants. Thrombolytic agents deployed in other studies were streptokinase,25 and recombinant tissue plasminogen activator (rtPA).26 27

Experimentally new thrombus is more sensitive to thrombolysis than old.28 The morphology of thrombus in CVT is essentially unknown and the time window for therapy is unexplored. Thrombotic agents have differing biological mechanisms and timing and choice are crucial to both safety and efficacy. rtPA has a high affinity for fibrin, its lytic properties being increased 400-fold when bound to
neither urokinase nor streptokinase show such fibrin specificity, both activating the plasminogen-plasmin system. These differing properties may explain the differing safety and efficacy results in cerebral arterial studies. The selection of agents studied in CVT has not been accompanied by a rationale for choice.

Tsai et al. retrospectively reviewed 29 patients with angiographically proved acute CVT. Of these patients, 18 received local urokinase, all had complete recovery except one who was left with mild deficits, six patients with severe CVT presenting in coma died with supportive treatment alone. Heparin was given to four patients, in whom three made a complete neurological recovery. No conclusion can be drawn from this study in that only patients with mild to moderate disease were treated. Frey et al. treated 12 patients with clinically disabling and non-resolving or worsening CVT with combined endovascular rtPA and intravenous heparin; of these, seven had evidence of haemorrhage on pretreatment MRI varying from subtle petechiae in four to evident haemorrhage in three patients. The emphasis of this report was on the restoration of the venous flow; the reporting of the final outcome was by neurological examination and the duration of hospital stay. In the six patients with recanalisation, five made a complete recovery and one had visual impairment from prolonged papilloedema. Of the three patients with partial recanalisation, two experienced symptomatic recovery and one had a persistent language disorder. A further three showed no restoration of the flow, one being functionally independent, one with right hemiparesis, and another with seizures at discharge. This study also showed that treatment induced or worsened symptomatic haemorrhagic transformation in two patients, at variance with other reports. Horowitz et al. reported no worsening symptomatic brain haemorrhage with urokinase infusion in 13 patients with CVT despite pretreatment haemorrhage in four. Kim and Suh reported no post-treatment haemorrhage in nine patients treated with rtPA. Smith et al. reviewed the English literature to 1997 and found 49 patients of whom 31 received supportive treatment and 18 heparin and/or local thrombolysis. The mortality was 12.5% in the heparin/thrombolysis group compared with 48% in the supportive group. The heterogeneity of these reported experiences, as well as the variable type and dose of thrombolytic agent, make it difficult to draw any conclusions on this treatment modality; importantly, the safety of such treatment is unclear. Case series with good outcomes from enthusiastic centres introduce reporting bias and further uncertainty. This invasive, potentially dangerous treatment has no clear evidence based rationale, being provided generally to the illest patients in centres with available interventional neuroradiological expertise (for summary of local thrombolysis reports, refer to table 2).

### Table 1
**Studies of heparin as treatment of cerebral venous sinus thrombosis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of the study</th>
<th>Patients (n)</th>
<th>Type of heparin</th>
<th>Dose of heparin</th>
<th>Outcome assessment</th>
<th>Follow up oral anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einhaupl et al. 1991</td>
<td>A mix randomised placebo-controlled and retrospective study</td>
<td>20 in the randomised part and 102 patients in the retrospective part</td>
<td>Intravenous unfractionated heparin</td>
<td>Bolus injection of 3000 IU followed adjusted dose heparin (25000–65000 IU/day).</td>
<td>A specially designed sinus venous thrombosis severity score for the randomised arm</td>
<td>None</td>
</tr>
<tr>
<td>Brucker et al. 1998</td>
<td>Retrospective study</td>
<td>42 Patients received heparin, no control group</td>
<td>Intravenous unfractionated heparin</td>
<td>Low dose, intermittent dose and adjusted dose heparin in the retrospective arm.</td>
<td>Modified Rankin scale</td>
<td>Heparin was followed by oral anticoagulant, duration was not specified</td>
</tr>
<tr>
<td>Bruin et al. 1999</td>
<td>Randomised placebo-controlled trial</td>
<td>60 Patients</td>
<td>Low molecular weight heparin</td>
<td>180 Anti-factor Xa units/kg/24 hour administered subcutaneous twice daily for 3 weeks</td>
<td>Barthel index of activities of daily living and Oxford handicap scale</td>
<td>3 Months of oral anticoagulant for patients allocated to low molecular weight heparin (open phase)</td>
</tr>
</tbody>
</table>

The future

The uncertain natural history, multiplicity of causes, and variable severity of clinical presentation results in current management being “case by case”. Death and disability seems primarily related to the extent of the venous infarction (and thus the extent and/or the site of venous occlusion) as well as age, associated or causal infection, and rapid clinical onset. There is little evidence on the importance of causation in predicting outcome, with the exception of obstetric cases. Given this uncertainty, many think that all cases of CVT should be treated with dose adjusted heparin irrespective of clinical status, cause, or CT appearance, with the further recommendation that local thrombolysis should be reserved for more extensive

### Table 2
**Cases reports of endovascular thrombolysis as treatment of cerebral venous sinus thrombosis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of the study</th>
<th>Patients (n)</th>
<th>Type of thrombolysis</th>
<th>Outcome assessment</th>
<th>Recanalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rocco et al. 1981</td>
<td>Case report</td>
<td>5</td>
<td>Urokinase</td>
<td>Neurological examination</td>
<td>Sinuses were fully patent in four patients. None were partially patent. Others did not have a follow up angiogram.</td>
</tr>
<tr>
<td>Smith et al. 1994</td>
<td>Case report</td>
<td>7</td>
<td>Urokinase</td>
<td>Neurological examination</td>
<td>Sinuses were fully patent in seven patients. Partially patent in four patients. Sinus were fully patent in nine patients.</td>
</tr>
<tr>
<td>Tsai et al. 1995</td>
<td>Retrospective study</td>
<td>29</td>
<td>Urokinase in 18 patients, and 11 patients received no treatment or heparin</td>
<td>Neurological examination</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Horowitz et al. 1995</td>
<td>Case report</td>
<td>12</td>
<td>Urokinase</td>
<td>Neurological examination</td>
<td>Sinuses were fully patent in seven patients. Partially patent in four patients. Sinus were fully patent in nine patients.</td>
</tr>
<tr>
<td>Kim and Ho Suh 1997</td>
<td>Case report</td>
<td>9</td>
<td>rtPA</td>
<td>Neurological examination</td>
<td>Sinuses were fully patent in six patients. Partially patent in three patients and no change in three patients.</td>
</tr>
<tr>
<td>Frey et al. 1999</td>
<td>Case report</td>
<td>12</td>
<td>rtPA</td>
<td>Neurological examination and the duration of the stay at hospital</td>
<td>Sinuses were fully patent in seven patients. Partially patent in four patients. Sinus were fully patent in nine patients.</td>
</tr>
</tbody>
</table>

Series of less than five patients were excluded.
disease and clinical worsening. Do we need to improve upon this advice bearing in mind that evidence for both heparin or thrombolysis is debatable, in terms of both safety and efficacy? Our survey of British neurologists would indicate "yes" with the need for further data on natural history and better designed trials comparing heparin, thrombolysis, and placebo. The first step is clearly to collect prospectively data on how patients currently present and are treated, their outcomes, and particular aetiologies. To this end, many of these issues are currently being considered by the International Study on Cerebral Vein and Dural Thrombosis (ISCVT). The object of this enterprise is to prospectively collect data on clinical presentation, cause and risk factors, prognostic indicators, currently applied treatments, and their complications and outcomes. This is a multicentre worldwide collaboration with the intention of following up cases over a 3 year period. Currently, data have been collected on 223 patients from 98 centres, although little, so far, has been reported from the United Kingdom. British neurologists, given their uncertainty, should be encouraged to participate in this venture and may contact the study group on iscvt@isgpt pt. (www.iscvt.com) for further information. It is only through such an observational study that the need for and the design of clinical trials can be addressed; in particular, risk stratification may allow outcome prediction and randomisation to appropriate trials—that is, heparin versus placebo, heparin versus thrombolysis. In the meantime, we would suggest that patients be managed on a case by case basis and would endorse Bousser’s view that thrombolysis should be reserved for those patients who continue to decline despite optimal supportive management with dose adjusted heparin.

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