

## Cerebral venous thrombosis: medical therapy

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This review concentrates on the medical therapy for aseptic cerebral venous thrombosis (CVT) presenting in its typical form. Raised intracranial pressure as the sole manifestation of cerebral venous disease will not be covered, nor will any reference be made to the management of the seizures that often complicate CVT.

Raised intracranial pressure is common in CVT, and there is little evidence that any form of medical treatment directly influences it. Therapies that have been advocated include dexamethasone, mannitol and therapeutic lumbar puncture. In one series<sup>1</sup>, steroids were used in 16 of 38 patients, though on what basis is not clear. The authors concluded that 'The judicious combination of antiedematous agents, water restriction, acetazolamide and repeated lumbar punctures can, in the great majority of cases, avoid the various surgical procedures that have been advocated, such as shunting or venous by-pass'. Since these medical measures have never been subject to objective scrutiny, their value is unproven.

### ANTICOAGULANT THERAPY

Anticoagulant therapy was proposed by Purdon Martin and Sheehan in 1941<sup>2</sup> and first used a year later in two patients with sinus thrombosis occurring within the first 10 days of delivery<sup>3</sup>. One of the patients survived, and was discharged well. Subsequently case-reports, or series, appeared in which anticoagulants had been used in no obviously structured pattern but with belief in their efficacy<sup>4,5</sup>. Contrary opinions were expressed, based on the experience of patients developing sometimes fatal intracerebral haemorrhage as a result of the treatment<sup>6</sup>.

The results of the first randomized trial of anticoagulant therapy in CVT were published in 1991<sup>7</sup>. In addition to a randomized study of 20 patients (10 on heparin, 10 on placebo), a retrospective analysis of 102 patients treated with heparin was done, particularly with respect to the incidence of intracranial haemorrhage. The 20 cases were derived from a total of 28 angiographically proven cases. The reasons for excluding 8 patients (7 of whom received heparin) were previous treatment with heparin (3), previous treatment with antiplatelet agents for headaches (3), hypertension (1) and consent not given (1). Dose-adjusted

heparin was used to achieve a target partial thromboplastin time (PTT) of 80–100 s. The treating physician was not blinded but the assessing physician was. The authors used a specially devised scale to assess outcome. The mean delay in initiating therapy from onset of symptoms was 32.5 days for the heparin group and 24.8 days for the control group.

The mean scores in the treated and untreated groups at 21 days were 0.6 and 3.9 ( $P < 0.005$ ). After 3 months, 8 treated patients had made a complete recovery and 2 had slight deficits. In the placebo group, 1 patient had recovered completely, 6 had neurological deficit and 3 had died. The paper attracted considerable criticism<sup>8,9</sup>. It was noted that the clinical features were sparsely described, that entry into the trial was relatively late and that the scoring system used was idiosyncratic. If analysis was based on the outcome at three months of either death or mild paresis, then the difference between the two groups did not reach significance ( $P \geq 0.09$ )<sup>9</sup>.

A further conclusion of this paper, though largely based on retrospective analysis, was that anticoagulant therapy was safe in patients with CVT even in the presence of pre-existing cerebral haemorrhage. This issue has been readdressed recently<sup>10</sup>. The study, again retrospective, assessed 18 patients with CVT and haemorrhagic infarction (HI) collected over 21 years. 6 of the patients were verified as having HI only at necropsy and were excluded. Of the remainder, half had received anticoagulants and half had not. Those not receiving anticoagulants had larger mean volumes of haemorrhage on computed tomography (CT), were often deteriorating clinically and in half the cases had midline shift. Indeed 2 proceeded to craniotomy. All that could be concluded was that, in a small group of patients with relatively small haemorrhagic infarcts, with no shift, who were stable (5/6) and whose haematoma was not expanding, anticoagulation appeared safe.

A further retrospective analysis of heparin treatment in acute cerebral sinus venous thrombosis was published in 1998<sup>11</sup>. 42 cases were identified retrospectively, spanning a 5-year period. Of these patients, 8 had experienced headache alone. In 22 cases haemorrhagic lesions were visible on the initial CT or magnetic resonance (MRI) examinations. All the patients had been treated with intravenous heparin (sufficient to double the partial thromboplastin time) for an average of three weeks, followed by oral anticoagulant therapy. The international

normalized ratio (INR) being sought was not given, nor was the total duration of anticoagulant therapy. The authors indicated that, in multiple follow-up MRI scans, they did not find any enlargement of pre-existing haematomas or haemorrhagic infarctions. One patient showed haemorrhagic transformation of an area of thalamic infarction but had no clinical sequelae.

A more extensive, prospective study of heparin treatment of CVT was required and is now published<sup>12</sup>. The diagnosis was confirmed by cerebral angiography or MRI. Patients with papilloedema and impaired vision requiring lumbar punctures or cerebrospinal fluid shunting were excluded. 60 patients were recruited, though one was subsequently eliminated because of incorrect diagnosis (arterial cerebral infarction). No patients were lost to follow-up. 12 of the 59 patients had isolated intracranial hypertension. 29 patients had evidence of cerebral haemorrhage on baseline CT or MRI, and 8 patients had non-haemorrhagic infarction. Superior sagittal sinus thrombosis was present in 88%. Treatment consisted of low-molecular-weight heparin in approximately 180 anti-factor-Xa units/kg per 24 hours in two daily subcutaneous injections, or placebo. After three weeks the treatment code was broken. Those on heparin received oral anticoagulants for ten weeks (INR 2.5–3.5), those on placebo received nothing. Outcome was based on two measures of activity, the Barthel index (BI) applied twenty-one days after randomization and the Oxford Handicap Scale (OHS) applied after twelve weeks. Randomization within ten days of onset of symptoms was achieved in 59%. There were four withdrawals from treatment, two of those in keeping with the protocol. Poor outcome (death or a BI under 15) was recorded in 20% of the treated and 24% of the placebo group. The death rates were 7% and 14%, respectively. After twelve weeks, poor outcome, defined as an OHS of  $\leq 3$ , was recorded in 13% of the treated group and 21% of controls. All 6 deaths occurred in patients with haemorrhage on the baseline CT but in none of these could death be attributed to a new or enlarged haematoma. None of the differences found in this study were statistically significant. The authors pointed out that no data were available for direct comparison between low-molecular-weight heparin (as they used) and unfractionated heparin (as used in the only other randomized study of CVT)<sup>7</sup>. By a combined analysis of the two studies a modest but not statistically significant benefit was detected in favour of heparin treatment. Despite this, the study has been greeted enthusiastically in at least one editorial<sup>13</sup>. The same editorial reviewed the role of local thrombolysis but found that it could not be recommended as first-line treatment. Surprisingly perhaps, the same reviewer concluded that a randomized trial of heparin versus heparin plus local thrombolysis was not a priority.

## SYSTEMIC THROMBOLYTIC THERAPY

The first report of systemic thrombolytic therapy in CVT concerned 5 patients treated with urokinase<sup>14</sup>. The authors reported a total of 10 patients, 2 of whom had ear infections. The rationale for treating only 5 with urokinase was not given. Of the 5, 4 received anticoagulant therapy in addition. Indeed, one of the 4 showed clinical extension of the disease on urokinase alone. Other authors were less enthusiastic, albeit often on the basis of a single personal case<sup>6</sup>. Combined heparin and urokinase treatment was subsequently reported in 5 patients with successful outcome<sup>15</sup>. After pretreatment with heparin, urokinase was given with heparin for two to six days followed by anticoagulation with heparin or oral agents for two months. All the patients recovered completely, and in 4 angiography showed recanalization of the affected veins.

## COMBINED HEPARIN AND INTRATHROMBUS THERAPY

That local thrombolytic therapy might offer an advantage over heparin is suggested by those case reports in which resolution of symptoms (and recanalization of obstructed sinuses) was achieved only when treatment was switched from one to another<sup>16</sup>.

Appraisal of the role of local thrombolytic therapy is complicated by those instances where it has been accompanied by heparinization. Frey *et al.*<sup>17</sup> have reported such a series, using a combination of heparin and recombinant tissue plasminogen activator (rt-PA). 12 consecutive patients, with symptoms of one to forty days' duration, were treated. Almost all the patients had thrombus in the superior sagittal, transverse and sigmoid sinuses in various combinations. 2 had a raised intracranial pressure alone. Flow was restored completely in 6, incompletely in 3 and not at all in the remainder. In 2 patients, treatment was associated with an enlargement of pretreatment intracerebral haematomas. The authors concluded, from their experience, that rt-PA should not be given to patients with a pretreatment haematoma in the range of 14 mL. They pointed out that patients with combined convexity and deep venous system thrombosis generally had a worse prognosis than those with convexity sinus thrombosis alone, and that the distribution of these two types of venous thrombosis had to be taken into account in analysis of individual reports.

## CONCLUSION

Heparin appears to be a safe treatment for patients with cerebral venous thrombosis, whether or not there is a pre-existing haematoma or haemorrhagic infarction. There are no data indicating whether low-molecular-weight heparin is a better option than conventional heparin. In

that low-molecular-weight heparin can be used in a standardized dose regimen according to the patient's weight, and in that it does not produce thrombocytopenia, it is probably the better option. Whether heparin significantly improves outcome in this disease remains uncertain. Peripheral thrombolytic therapy has never been subject to a properly organized trial. The risks of inducing haemorrhage are substantially higher than with local therapy and this treatment option should probably not be recommended. Local thrombolytic therapy, when tried, has always been combined with heparin. No controlled trials have been conducted and the methodology and dosage have varied. Any further trials of treatment in CVT (and undoubtedly these are needed) will have to take account of risk factors that influence outcome. Patients with raised intracranial pressure alone have a better prognosis than those with evidence of parenchymal damage, while involvement of the deep venous system, as opposed to the convexity veins, carries a worse prognosis.

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