Heparin treatment in sinus venous thrombosis

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Treatment of sinus venous thrombosis (SVT) is controversial. Although heparin has been used for this condition, many investigators have opposed its use because of the frequent occurrence of intracranial haemorrhage (ICH) in SVT. Therefore we have evaluated anticoagulation with adjusted-dose intravenous heparin for treatment of aseptic SVT in a randomised, blinded (patient and observer), placebo-controlled study in 20 patients (10 heparin, 10 placebo). The clinical course of the two groups, as judged by a newly designed SVT-severity scale, started to differ in favour of the heparin group after 3 days of treatment (p < 0.05, Mann-Whitney U-test) and the difference remained significant (p < 0.01) after 8 days of treatment. After 3 months, 8 of the heparin-treated patients had a complete clinical recovery and 2 had slight residual neurological deficits. In the placebo group, only 1 patient had a complete recovery, 6 patients had neurological deficits, and 3 patients died (p < 0.01, modified Fisher's exact test). An additional retrospective study on the relation between heparin treatment and ICH in SVT patients was based on 102 patients, 43 of whom had an ICH. 27 of these patients were treated with dose-adjusted, intravenous heparin after the ICH. Of these 27 patients, 4 died (mortality 15%), and 14 patients completely recovered. Of the 13 patients that did not receive heparin after ICH, 9 died (mortality 69%) and only 3 patients completely recovered. We conclude that anticoagulation with dose-adjusted intravenous heparin is an effective treatment in patients with SVT and that ICH is not a contraindication to heparin treatment in these patients.

Introduction

Treatment of sinus venous thrombosis (SVT) is controversial. Because no controlled clinical study has been reported, therapeutic recommendations are based on pathophysiological considerations, case-reports, or case-report series. Glucocorticoids,1-3 diuretics,4 osmotherapy,1 platelet inhibitors,5,6 surgical intervention,7-9 pentobarbital-induced coma,10 and systemic11-12 or local13 thrombolytic therapy have been suggested. Since the first successful use of heparin for treatment of SVT nearly 50 years ago, many investigators1,10-12 have strongly opposed its use because of the frequent spontaneous occurrence of intracranial haemorrhage (ICH) in SVT, as in arterial thrombosis.18-23 Recent retrospective studies, however, suggest that there may be a beneficial effect of heparin treatment:24,25 Dörstelmann et al20 reported two cases of superior sagittal sinus thrombosis with ICH who were treated successfully with heparin.

In 1977, we started a prospective study of the clinical spectrum of SVT. In the first 5 years, according to current recommendations, we did not use anticoagulation treatment. Although we recorded a high mortality during this period, we were surprised by the clinical recovery of 2 patients with SVT who were treated with intravenous heparin because of extracranial life-threatening thrombosis. This stimulated us to carry out a randomised, placebo-controlled, blinded trial of the therapeutic effect of heparin. We here report the results of the placebo-controlled study. Additionally, we have retrospectively analysed the

REFERENCES

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effect of heparin treatment on the occurrence of ICH in SVT and on the prognosis in SVT after haemorrhage.

**Patients and methods**

**Patients**

Period I—From 1977 to 1982, our treatment policy only allowed intravenous heparin in SVT patients for life-threatening extracranial thrombus. During this period, 35 patients with SVT were treated in our department—2 with dose-adjusted intravenous heparin (at least doubling of partial thromboplastin time [PTT]), 8 with low-dose heparin, 12 with heparin intermittently (eg, intermittent low-dose or short-term high-dose), and 13 who did not receive heparin.

Period II (controlled study period)—From April, 1982, to February, 1984, a randomised, blinded (patient and observer), placebo-controlled trial of dose-adjusted intravenous heparin was done. 28 patients with angiographically proven SVT were seen during this period. 20 of the patients were included in the randomised study (10 placebo, 10 intravenous heparin), and 8 patients were excluded (see table). Of the excluded patients, 6 received dose-adjusted intravenous heparin, 1 low-dose heparin, and 1 no heparin.

Period III—After this trial, intravenous dose-adjusted heparin became our standard treatment. We saw an additional 39 patients from March, 1984, to May, 1985. 38 were treated with intravenous heparin, none with low-dose heparin, and 1 no heparin (high arterial blood pressure as contraindication to heparin treatment).

**Methods**

Diagnostic criteria of SVT—The diagnosis of SVT was made by arteriographic angiography. Our diagnostic criteria required both direct and indirect signs of thrombosis, including nonvisualisation of a sinus, part of a sinus, or vein (direct signs), and presence of cork screw veins, broken bridging veins, venous dilation, venous collaterals, and delayed venous emptying (indirect signs). Diagnosis was confirmed by necropsy in 2 patients. The strict diagnostic criteria may have led to the exclusion of some patients with SVT, especially those with thrombosis of a lateral sinus. However, we think a firm diagnosis of SVT is mandatory when anticoagulation is prescribed. A life-threatening haemorrhage or thrombocytopenia in a heparin-treated patient were regarded as reasons to discontinue heparin treatment. A life-threatening extracranial thrombosis was regarded as a reason to discontinue placebo and to start anticoagulation treatment. The primary endpoint of the study was clinical outcome. Patients were clinically assessed daily by a physician who had no knowledge about the treatment assignment. For standardised assessment, we used a specially developed sinus venous thrombosis severity scale.

Exclusion criteria—Not included were patients with mechanical occlusion of a sinus or vein (eg, tumours), intracranial tumours or angiomata, septic SVT, cavernous sinus thrombosis, age less than 10 years, and dubious angiographic findings.

Cranial computed tomography (CCT)—In addition to angiography, one or more CCTs were done in all patients (for CCT findings in SVT see ref 27).

Controlled study—All patients diagnosed with aseptic SVT after April 1, 1982, were eligible for this study. Exclusion criteria included pretreatment with anticoagulate or with platelet inhibiting drugs (such as aspirin), malignant disease, haemorrhagic diathesis, terminal renal insufficiency, liver disease with reduced synthesing capacity, an extracranial indication for heparin treatment, and the usual contraindications for heparin treatment. By these criteria, 8 patients were excluded because of hypertension (1 patient), previous treatment with heparin in another hospital (2), previous treatment with heparin because of multiple venous and arterial catheterisation (1), previous treatment with platelet agents for headache (3), and consent not given (1). Patients or relatives were informed about the study and asked for informal consent. Patients were then allocated to either the heparin or the control group by means of numbered sealed envelopes, which contained the treatment assignment. Random assignment was provided by a computer random number generator. Heparin treatment was started with an intravenous bolus injection of 3000 IU and continued with 25 000-65 000 IU/day continuous intravenous infusion. The heparin dose was adjusted so that the initial PTT was started with an intravenous bolus injection of 3000 IU and continued with 25 000-65 000 IU/day continuous intravenous infusion. The heparin dose was adjusted so that the initial PTT was at least doubled but did not exceed 120 s (the target PTT was 80–100 s). PTT was measured at least twice a day. The patients in the placebo group received continuous saline infusions. The treating physician, but not the patient, was informed about treatment assignment; a true double-blind study was not possible because the treating physician of any patient must know whether anticoagulation is prescribed. A life-threatening haemorrhage or thrombocytopenia in a heparin-treated patient were regarded as reasons to discontinue heparin treatment. A life-threatening extracranial thrombosis was regarded as a reason to discontinue placebo and to start anticoagulation treatment. The primary endpoint of the study was clinical outcome. Patients were clinically assessed daily by a physician who had no knowledge about the treatment assignment. For standardised assessment, we used a specially developed sinus venous thrombosis severity scale.

![Fig 1 — Clinical course during first three weeks of treatment](https://example.com/fig1.png)

Data are presented as means of SVT severity score for the control group (open circles) and the heparin (closed circles) group. Score 0=no symptoms; score 9=death. Bars are SEM.

### TABLE 1

**BASELINE DATA OF PATIENTS IN CONTROLLED TRIAL (PERIOD II)**

<table>
<thead>
<tr>
<th></th>
<th>Heparin group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.3 (12.2)</td>
<td>37.2 (18.9)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/6</td>
<td>5/5</td>
</tr>
<tr>
<td>Start of therapy</td>
<td>32.5 (60.8)</td>
<td>24.8 (41.8)</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>12.1 (3.9)</td>
<td>13.9 (2.8)</td>
</tr>
<tr>
<td>SVT Scale Score</td>
<td>40 (2.1)</td>
<td>35 (1.5)</td>
</tr>
<tr>
<td>No of patients with ICH</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are mean (SD).
Additionally, a CCT was done when the clinical examination raised suspicion of ICH. The study was planned for 60 patients with control group. Deficit, death was regarded as a reason to discontinue the study.

The mean SVT severity score at the beginning of treatment was 4-0 (median 3) in the heparin group compared with 3-5 (3) in the control group. After 3 days, the mean score in the heparin group was 2-9 (2-5) and in the control group 3-8 (3-5) (p < 0.05, Mann-Whitney U-test for change in SVT severity score). After 8 days of treatment, mean scores were 1-5 (0-5) and 3-6 (3), respectively (p < 0.01), and after 21 days, 0-6 (0) and 3-9 (2-5), respectively (p < 0.005). The clinical course of each patient is shown in fig 2. After 3 months, 8 patients in the heparin group had a complete clinical recovery and 2 had slight neurological deficits. In the control group, only 1 patient completely recovered, 6 patients had neurological deficits, and 3 patients died. The difference between the two groups is statistically significant (p < 0.01, modified Fisher's exact test).

Complications—Complications in the heparin group included haematuria in 1 patient, a haematoma after puncture of the femoral artery in another patient, and a stillbirth of a 38-week-old fetus in a pregnant woman. Heparin treatment was not stopped in these patients. In the control group, 1 patient had severe pulmonary infarction. This patient was subsequently given heparin, but died 2 hours later of cardiac arrest.

ICH—At the beginning of treatment, CCTs of 3 patients in the heparin group and of 2 in the control group showed an ICH. In the heparin group, no additional ICH was detected during the treatment period. In the control group, 3 patients had an ICH during treatment, 2 of whom had not had an ICH at the beginning of therapy. 2 of the 3 patients in the heparin group with ICH at the start of the treatment had a complete clinical recovery. The other patient had only a slight neurological deficit after 3 months. Both patients in the control group with ICH at the start of treatment died.

Retrospective study on ICH and heparin treatment

Since our findings from the controlled study only gave a trend with respect to the relation between heparin and ICH, we did a retrospective study of all patients with SVT whom we had treated from 1977 to May, 1991. This was a retrospective analysis based on all 102 patients with angiographically proven SVT seen during this period. In this historical control study, patients treated with dose-adjusted intravenous heparin were compared with those treated without heparin. The control group consisted of patients treated during period I and of patients who received placebo during the controlled study (period II). The heparin group consisted of patients who received heparin during the controlled study and most of the patients treated after February, 1984 (period III), when dose-adjusted intravenous heparin became our standard therapy.

We would like to emphasise that there is a time and experience bias of the patients treated after February, 1984 (period III), when dose-adjusted intravenous heparin became our standard therapy. Of the 27 patients receiving dose-adjusted intravenous heparin after ICH, 4 died (mortality 15%), 2 had a severe neurological deficit, 7 mild neurological deficits, and 14 had complete clinical recoveries. 9 of 13 patients receiving no heparin after ICH died (mortality 69%), 1 had a mild neurological deficit, and 3 patients had complete recoveries. 3 patients received low-dose heparin after ICH, of whom 1 had a mild neurological deficit and 2 recovered completely.

Discussion

Our findings show a statistically significant beneficial effect of heparin treatment in SVT, which was seen after 3 days of therapy and confirmed at every subsequent examination up to 3 months after the start of the treatment. An analysis of the concomitant medication during the treatment period revealed that corticosteroids were given to 3 patients of the control group but to none of the heparin group. Since corticosteroids may worsen the thrombosis, this difference requires a closer examination. Of the 3 patients were treated with corticosteroids after clinical deterioration as a last resort in a late stage of the disease. The
third patient had a complete clinical recovery. Thus, we conclude that treatment with corticosteroids cannot account for the difference in clinical outcome between the two groups.

Moreover, the retrospective study showed that the mortality in patients with ICH receiving heparin was much lower than that in patients receiving no heparin. Although there was a bias in the data because patients without heparin were mostly treated earlier, we do not believe that this potential bias can fully account for the difference in outcome (mortality 15% heparin vs 69% no heparin).

The data comparing the occurrence of ICH during close-adjusted intravenous heparin treatment (2 of 56 patients treated with dose-adjusted intravenous heparin), low-dose or intermittent heparin treatment (8), and no heparin treatment (33) cannot be regarded as true incidence data because the observation time varied for the different groups. However, the data strongly suggest that close-adjusted intravenous heparin treatment does not promote ICH.

We therefore conclude that heparin is an effective treatment for SVT, that a diagnosis of ICH is not a contraindication for heparin treatment in SVT. Our results accord with recent reports in which a beneficial effect of heparin treatment in SVT were shown.5,24--26 Bousser et al23 reported that none of the 23 patients who were treated with intravenous heparin died. In 3 patients who were deteriorating despite other treatments, a striking improvement was seen the day after the onset of heparin administration. I of these patients had a haemorrhagic infarct on CT scan.

The effect of heparin, which can usually be seen within the first days of treatment, may be too slow to help the subgroup of patients with rapidly progressing thrombosis which involves large parts of the cerebral venous system and which rapidly leads to diffuse brain swelling and multiple haemorrhages. In such cases, intravenous thrombolytic therapy or local application of a thrombolytic agent13 may be indicated.

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REFERENCES

11. Di Rocco C, Iannelli A, Leone G, Moschini M, Valori VM. Heparin-

From The Lancet

Drug in the market?

Among the niceties of therapeutics nothing perhaps is more irregular, more irrational, or unscientific than the custom of administering powerful drugs in the form of lozenges or sweetmeats. Again and again has the custom of self-medication resulted in the most disastrous consequences to those who practise it, yet it is in these days a flourishing fashion. In its more open forms it is of too clearly injurious tendency to find much favour at the hands of the profession. We cannot but regret, therefore, that in the pharmacopoeial sanction of the drained sweetmeat it should appear to possess a species of medical recommendation, for, however we may disguise the fact, there can really be no question that the art of the confectioner is throughout a bid for popular custom. Its employment in the preparation of potent remedies we cannot but regard as a mistake. In appearance, if not intention, it suggests a needless transfer of professional responsibility, the consequence of which it is impossible to forecast. As a recent illustration of the serious mischief which may arise from this practice we may notice the case of a child who was recently poisoned by helping himself to a packet of the well-known trochisci morphiae which had been prescribed for his father. There is danger, though less, for the parent as well as the child in this mode of prescription. No doubt it may be modified by specific directions as to use, but even thus it is hardly possible to invest with any permanent and adequate suggestion of danger the familiar aspect of a lozenge. This form of remedy is now as well as the child in this mode of prescription. No doubt it may be