Randomized, Placebo-Controlled Trial of Anticoagulant Treatment With Low-Molecular-Weight Heparin for Cerebral Sinus Thrombosis

S.F.T.M. de Bruijn, MD; J. Stam, MD; for the Cerebral Venous Sinus Thrombosis Study Group

Background and Purpose—Treatment of cerebral sinus thrombosis with heparin is controversial. We conducted a double-blind, placebo-controlled multicenter trial to examine whether anticoagulant treatment improves outcome in patients with sinus thrombosis.

Methods—Patients were randomized between body weight–adjusted subcutaneous nadroparin (180 anti–factor Xa units/kg per 24 hours) and matching placebo for 3 weeks (double-blind part of trial), followed by 3 months of oral anticoagulants for patients allocated nadroparin (open part). Patients with cerebral hemorrhage caused by sinus thrombosis were also included.

Results—Sixty patients were enrolled, and none were lost to follow-up. In 1 patient the diagnosis proved wrong after randomization. After 3 weeks, 6 of 30 patients (20%) in the nadroparin group and 7 of 29 patients (24%) in the placebo group had a poor outcome, defined as death or Barthel Index score of $15$ (risk difference, $-4\%$; 95% CI, $-25$ to $17\%$; NS). After 12 weeks, 4 of 30 patients (13%) in the nadroparin group and 6 of 29 (21%) in the placebo group had a poor outcome, defined as death or Oxford Handicap Score of $\geq 3$ (risk difference, $-7\%$; 95% CI, $-26$ to $12\%$; NS). There were no new symptomatic cerebral hemorrhages. One patient in the nadroparin group had a major gastrointestinal hemorrhage, and 1 patient in the placebo group died from clinically suspected pulmonary embolism.

Conclusions—Patients with cerebral sinus thrombosis treated with anticoagulants (low-molecular-weight heparin followed by oral anticoagulation) had a favorable outcome more often than controls, but the difference was not statistically significant. Anticoagulation proved to be safe, even in patients with cerebral hemorrhage. (Stroke. 1999;30:484-488.)

Key Words: anticoagulants • randomized controlled trials • sinus thrombosis

Cerebral venous and sinus thrombosis is a rare but alarming disease that usually begins with severe headache. Sinus thrombosis may cause cerebral venous infarcts, which are frequently hemorrhagic and may lead to epilepsy, neurological deficits, or death. Obstruction of the sinuses often causes intracranial hypertension due to impaired drainage of the cerebrospinal fluid, which may cause optic nerve papilledema and impaired vision. On the other hand, sinuses, particularly the lateral sinus, can be occluded without any infarct or intracranial hypertension. In many patients the disease runs a benign course.1 Prothrombotic states, both hereditary and acquired (eg, protein C or S deficiency, factor V Leiden mutation, pregnancy, and puerperium), are regarded as risk factors, but in many cases the cause remains unknown.2

The treatment of sinus thrombosis with heparin is controversial. Heparin may arrest progression of thrombosis and prevent further infarction. It may also cause hemorrhages in infarcted brain tissue, with increased neurological deficits, although well-documented cases are scarce. In the only previous randomized trial,3 unfractionated heparin was compared with placebo in 20

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patients. The authors concluded that heparin was a safe and effective treatment for sinus thrombosis, but the results have been disputed because of the small sample size, the long treatment delay, and questionable outcome criteria.4,5 We conducted a double-blind, placebo-controlled multicenter trial to investigate whether anticoagulant treatment with a therapeutic dose of low-molecular-weight heparin improves outcome in patients with sinus thrombosis.

Subjects and Methods

Patients

All patients with clinically suspected cerebral venous sinus thrombosis confirmed by cerebral angiography or by MRI (including MR angiography) were eligible. Reasons for exclusion were age of <18 years, pregnancy, indications for or contraindications against heparin, conditions with a poor prognosis unrelated to sinus thrombosis, papilledema with impaired vision that required lumbar punctures or cerebrospinal fluid shunting, or recently performed lumbar puncture or surgical procedure. Indications for heparin were leg-vein throm-
basis or pulmonary embolism. Contraindications against heparin were bleeding disorders, thrombocytopenia (<100×10^9/L), hepatic or renal dysfunction, uncontrolled hypertension (diastolic >110 mm Hg), or recent gastrointestinal hemorrhage. Cerebral hemorrhage caused by sinus thrombosis was no reason for exclusion. The study was approved by the ethics committee at each center. Informed consent by the patient or next-of-kin was obtained before inclusion.

**Treatment**

Treatment consisted of nadroparin in a dose of approximately 180 anti–factor Xa units/kg per 24 hours or matching placebo, administered by 2 daily subcutaneous injections. Other drugs with effects on coagulation were not allowed. Graduated compression stockings were recommended to prevent leg vein thrombosis.6 If a lumbar puncture was necessary, the trial medication was stopped 24 hours before and after the procedure. One such interruption was allowed in each patient. Reasons to stop trial medication were major extracranial hemorrhage, a symptomatic new intracranial hemorrhage confirmed by CT scan, the need for repeated lumbar punctures or surgical intervention, and confirmed leg-vein thrombosis or pulmonary embolism. After 3 weeks the treatment code was broken (see below), and patients allocated to nadroparin were to receive oral anticoagulants for 10 weeks (target: international normalized ratio between 2.5 and 3.5). Patients on placebo did not receive follow-up anticoagulant treatment.

**Outcome Assessments**

The Barthel Index (BI) of activities of daily living (from 1 [totally dependent] to 20 [fully independent]), assessed by the attending physician at day 21 after randomization when treatment assignment was still masked, was used to define the primary outcome measure. Poor outcome was defined as BI of 15 or less, or death. Secondary outcome measure was the Oxford Handicap Scale (OHS) after 12 weeks (not blinded),3 in which we dichotomized between death or (partial) dependence (grade 3 to 5) and minor handicap or better (grade 0 to 2). We also assessed the BI score after 12 weeks. Safety was examined by recording any new symptomatic CT-confirmed intracranial hemorrhage, all extracranial hemorrhages, and confirmed leg vein thrombosis or pulmonary embolism. Major bleeding complications were defined as clinically manifest hemorrhages that caused a fall in hemoglobin of 1.2 mmol/L (2 g/dL) or more; retroperitoneal or intraocular hemorrhages; and hemorrhages that required transfusion or surgery. All other bleeding was considered minor.

**Sample Size and Statistics**

The sample size was based on an expected incidence of 40% poor outcomes,8–12 and a large expected treatment effect as suggested by the results of the previous trial.3 To detect a reduction to 10%, poor outcomes at a 5% level of significance (2 tailed) with a power of 80% a study size of 60 patients is needed. The primary analysis was performed by the safety committee.

**Randomization and Stratification**

Participating centers contacted the central study coordination center if patients met all inclusion and exclusion criteria. Patients were randomized centrally, by means of a computer generated allocation schedule. We applied stratified block randomization, with separate allocation sequences for 3 strata: patients with hemorrhage on the pretreatment CT scan; patients with chronic (>30 days) intracranial hypertension (defined as headache, a CSF pressure of more than 20 cm water, and no other symptoms); all other patients. In view of the small sample size and the relatively large number of centers, a very small block size of 2 was used within strata. To minimize overall imbalance, the probability of the first allocation in each block was based on the total amount of imbalance in the number of allocated patients up to that point. In spite of this procedure, an imbalance was observed after 30 patients had been randomized (21 patients randomized to placebo), due to a technical error in the computer program. To correct this, 3 new blocks (1 in each stratum) were defined in the allocation schedule. The number of allocations in each block was based on the amount of imbalance plus one, leaving a random component in the allocation procedure. The block size and the temporary imbalance were not disclosed to the participating physicians.

**Allocation Concealment: Masking**

Masking was achieved by using prefilled syringes with nadroparin or an identically appearing placebo solution. The randomization program allocated a unique number to each patient. This number corresponded to a package containing study medication. The treatment code was kept by the trial pharmacist in the coordinating center. After 3 weeks the treating physician faxed the primary outcome data to the trial center. Subsequently, the study coordinator obtained the treatment code from the trial pharmacist, and informed the physician about continuing anticoagulant therapy.

**Results**

Between July 1992 and November 1996 sixty patients were recruited from 14 hospitals in the Netherlands and the United Kingdom. We did not collect data on patients who were not eligible. No patients were lost to follow-up (Figure 1). One patient was ineligible due to an incorrect diagnosis (arterial cerebral infarction), discovered 1 day after randomization. There were no important differences in clinical characteristics at baseline between the 2 study groups (Table 1). Thirty-five patients (59%) had an onset within a time period of 10 days between the first symptoms and the time of randomization. In 9 patients there was an acute onset of ≤3 days. Twelve patients had isolated intracranial hypertension. There were no cases of chronic (>30 days) intracranial hypertension.

Overall, 29 patients had signs of cerebral hemorrhage on their baseline CT or MRI scans, and 8 patients had nonhemorrhagic infarction. MR imaging or conventional angiography...
showed involvement of the superior sagittal sinus in 50 cases (88%); in 14 of them the straight sinus was also involved. Overall, the straight sinus was thrombosed in 17 cases (29%). The most frequent etiologic conditions were puerperium (7 patients, 12%), use of oral contraceptives (35 patients, 59%), and carriership of hereditary prothrombotic factors (9 patients, 15%; Table 2).

In 2 patients, 1 in the nadroparin group and 1 in the placebo group, trial medication was stopped and replaced with intravenous unfractionated heparin by the treating physician. In 2 other patients, trial medication was stopped in agreement with the protocol: 1 patient (nadroparin group) had a major gastrointestinal hemorrhage, and 1 (placebo group) needed repeated lumbar punctures. In 2 patients (1 nadroparin, 1 placebo), trial treatment was interrupted for 48 hours for a lumbar puncture.

### Outcome
Six of 30 patients (20%) treated with nadroparin and 7/29 control patients (24%) had a poor outcome (death or BI score of <15) after 3 weeks (risk difference, −4%; 95% CI, −25 to 17; Table 2). Six patients died, 2 (7%) in the nadroparin group and 4 (14%) in the placebo group. All deaths occurred within 2 weeks after inclusion (range, from days 1 to 14).

After 12 weeks, 4 patients (13%) in the nadroparin group and 6 controls (21%) had a poor outcome on the predefined secondary outcome measure of death or dependence, defined as an OHS score of ≤3 (risk difference, −7%; 95% CI, −26 to 12%). Using the same definition as for the primary outcome (death or BI score <15) 3 patients on nadroparin (10%) had poor outcomes versus 6 controls (21%) (risk difference, −11%; 95% CI, −29 to 7%).

### TABLE 2. Etiology and Possibly Associated Conditions

<table>
<thead>
<tr>
<th>Acquired prothrombotic conditions</th>
<th>Nadroparin (n=30)</th>
<th>Placebo (n=29)</th>
<th>All Patients (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerperium</td>
<td>7/59</td>
<td>35/59</td>
<td>42/59</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>35/59</td>
<td>62/59</td>
<td>97/59</td>
</tr>
<tr>
<td>Antiphospholipid antibodies*</td>
<td>6/42</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Secondary to systemic disease</td>
<td>4/59</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Hereditary prothrombotic deficiencies</td>
<td>9/59</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Factor V Leiden mutation*</td>
<td>7/51</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Protein C deficiency*</td>
<td>2/51</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Spinal dural puncture</td>
<td>2/59</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>No cause</td>
<td>10/59</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Percentage based on incomplete data.

*Except for papilledema scored in the noncomatose patients (n=50).

†Could not be assessed in the remaining patients.
A maximal BI score (no limitations in activities of daily living) was observed in 20 patients (67%) treated with nadroparin and in 21 on placebo (72%) after 3 weeks (Figure 2).

After 12 weeks these numbers were 27 (90%) and 23 (79%), respectively. However, many of these patients still had residual symptoms or even minor handicaps. If complete recovery is defined as being entirely without symptoms (OHS grade 1), only 6 patients in the active treatment arm (12%) and 8 of the controls (28%) were cured.

All 6 deaths occurred in the subgroup of 29 patients with hemorrhage on their baseline CT scan, but in none could death be attributed to new or enlarged cerebral hemorrhage. Fifteen patients in this subgroup received nadroparin and 14 placebo, with poor outcome after 3 weeks in 5 (33%) and 6 (43%), respectively (risk difference, −10%; 95% CI, −45% to 26%). Among the 30 patients without hemorrhage, only 2 had a poor outcome after 3 weeks, 1 after nadroparin and 1 after placebo. The patient withdrawn after randomization because of an incorrect diagnosis (allocated placebo) had a good outcome after 3 and 12 weeks.

**Adverse Events**

New symptomatic cerebral hemorrhages did not occur. One patient on nadroparin had a major gastrointestinal hemorrhage. Four patients in each treatment group had a minor extracranial hemorrhage. Skin hemorrhages at the injection site were recorded 5 times in the nadroparin group and once in the placebo group. There were no confirmed thromboembolic complications, but 1 patient on placebo died suddenly from (suspected) pulmonary embolism.

**Discussion**

Patients with sinus thrombosis treated with nadroparin followed by oral anticoagulants had better outcomes than control patients, but the large treatment effect suggested previously could not be confirmed. Although none of the differences we found were statistically significant, there is a trend for all predefined outcomes in favor of anticoagulation that would be clinically important if confirmed. Anticoagulation appeared safe, even in patients with cerebral hemorrhage caused by sinus thrombosis.

The only other published randomized trial was set up to include 60 patients, but recruiting was stopped after 20 patients. There was a statistically nonsignificant reduction of mortality in the patients treated with heparin (0/10 deaths in the heparin group versus 3/10 in the placebo group). The interpretation of this trial is complicated by the use of a grading system that counted patients in the placebo group with mild sequelae as poor outcomes and by the long delay before the treatment was started (means of 33 and 25 days for the heparin and placebo groups, respectively).

The delay between onset of symptoms and treatment in our study (mean, 10.6) is much shorter. A higher clinical awareness of sinus thrombosis, combined with the possibility of noninvasive confirmation by MRI, may have led to inclusion of less-severe cases. On the other hand, the proportion of patients in coma was similar in both studies, and we included more patients with some degree of hemorrhage (49% versus 25%). Therefore, we do not believe the difference between our results and those from the previous trial can be explained by important differences in patient characteristics.

We used subcutaneous low-molecular-weight heparin in a therapeutic dose instead of intravenous unfractionated heparin. No data are available that allow direct comparison of low-molecular-weight heparins versus unfractionated heparin in the treatment of cerebral sinus thrombosis. Randomized trials in patients with leg vein thrombosis or pulmonary embolism show that low-molecular-weight heparins, nadroparin included, are as effective as unfractionated heparin and cause fewer hemorrhagic complications. An additional advantage is that low-molecular-weight heparin can be given in fixed doses, only adjusted for body weight, without laboratory monitoring.

There were no new symptomatic cerebral hemorrhages in our study, which is remarkable in a condition characterized by a high rate of venous hemorrhagic infarcts. There were no confirmed thromboembolic complications, but 1 patient in the placebo group died from a clinically suspected pulmonary embolus. Pulmonary embolism associated with sinus thrombosis, caused by embolization from the cerebral sinuses or from concurrent leg-vein thrombosis, has been reported. The prevention of pulmonary embolism is probably an important benefit of anticoagulant treatment in patients with sinus thrombosis.

Some minor problems occurred during the course of the trial. There were 2 protocol violations, but on-treatment analysis (data not shown) does not alter the conclusion. The diagnosis was found to be wrong after inclusion in 1 case, although state-of-the-art diagnostic procedures were used in all patients. The diagnosis of sinus thrombosis with angiography or MRI can sometimes be difficult, but in the large majority of patients the diagnosis can be made reliably with these techniques.
unblinding in some cases. More hemorrhages at the injection site were reported in the nad roparin group, which may have influenced the judgment of outcome. The open design after 3 weeks may have introduced bias in the 3-month assessment.

The small size of the trial implies that moderate effects in favor of treatment (if present) could not be reliably confirmed or refuted. The sample size was based on the large treatment benefit suggested before\(^3\) and on the large proportion of patients with poor outcomes in published case series at the time of the start of the study.\(^8\) –\(^12\) The present series and other recent series show that patients with cerebral sinus thrombosis have a better outcome in terms of mortality or handicap than was previously reported. Recruitment was limited, as we anticipated, by the rarity of the condition. Nevertheless, the trial was 3 times larger than the only other randomized trial.

If we combine the results of both trials in a meta-analysis, the summary risk difference is a mortality reduction of 14.3% with heparin treatment (95% CI, −36 to 6%; random effects model of Der Simonian and Laird\(^{18}\)). The outcome “death or dependence” occurred in 4 of 40 of the anticoagulated patients (10%) and in 9 of 39 controls (23.1%), which gives a combined risk difference of −15.5% (95% CI, −37 to 6). Thus, a meta-analysis of both trials shows a modest but clinically important (but not statistically significant) benefit of any heparin treatment for sinus thrombosis. Approximately 300 patients would have to be recruited in a new trial to reliably confirm the treatment effect estimated in the meta-analysis. It seems unlikely that such a trial will be realized in the near future.

Based on our results and previous randomized data, we conclude that anticoagulant treatment with heparin is probably safe and beneficial for patients with sinus thrombosis, even those with intracranial hemorrhages.

Appendix: Sinus Thrombosis Study Group
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References
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