Endovascular Thrombectomy and Thrombolysis for Severe Cerebral Sinus Thrombosis
A Prospective Study

Jan Stam, MD, PhD; Charles B.L.M. Majoie, MD, PhD; Otto M. van Delden, MD, PhD; Krijn P. van Lienden, MD, PhD; Jim A. Reekers, MD, PhD

Background and Purpose—Most patients with cerebral sinus thrombosis (CST) recover after treatment with heparin, but a subgroup has a poor prognosis. Those patients may benefit from endovascular thrombolysis.

Methods—Prospective case series. Patients with sinus thrombosis were selected for thrombolysis if they had an altered mental status, coma, straight sinus thrombosis, or large space-occupying lesions. Urokinase was infused into the sinuses (bolus 120 to 600 x 10^3 U; then 100 x 10^3 U/h) via a jugular catheter, in 15 cases combined with mechanical thrombus disruption or removal.

Results—We treated 20 patients (16 women), mean age 32 years. Twelve patients were comatose and 14 had hemorrhagic infarcts before thrombolysis. Twelve patients recovered (Rankin score 0 to 2), 2 survived with handicaps, and 6 died. Factors associated with a fatal outcome were leukemia (3/6 versus 0/14, \( P = 0.02 \)) and large hemorrhagic infarcts (4/6 versus 2/14, \( P = 0.04 \)). Seizures were less frequent in the fatal cases (\( P = 0.05 \)). Patients who died had a larger mean lesion surface than survivors (30.5 versus 13.6 cm^2; \( P = 0.03 \)), larger midline shift (5.2 versus 1.7 mm; \( P = 0.02 \)), and a more rapid course (2.7 versus 8.2 days; \( P = 0.01 \)). Five patients who died had large hemispheric infarcts and edema before thrombolysis, causing herniation. Five patients had increased cerebral hemorrhage (3 minor, 2 major) after thrombolysis.

Conclusions—Thrombolysis can be effective for severe sinus thrombosis, but patients may deteriorate because of increased cerebral hemorrhage. Patients with large infarcts and impending herniation did not benefit. (Stroke. 2008;39:1487-1490.)

Key Words: sinus thrombosis ■ intracranial ■ thrombolytic therapy

Cerebral sinus thrombosis is usually treated with anticoagulation. The efficacy of conventional or fractionated heparin showed a modestly beneficial effect in 3 small randomized trials.\(^1\)\(^-\)\(^3\) Metaanalysis showed a pooled relative risk reduction of 0.46 for the outcome death or dependency after heparin compared to placebo (95% confidence interval 0.16 to 1.31).\(^4\) Most neurologists now use full-dose heparin (conventional or fractionated low-molecular weight [LMW]) as standard initial treatment for patients with CVST.\(^5\)

In the clinical trials 10% of the patients treated with heparin had a poor outcome. In a large prospective study of 624 patients, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), 13.4% had a poor outcome (dead or dependent, Rankin 3 or worse).\(^5\) Most patients (83%) were treated with heparin. Factors associated with a poor outcome were age (>37 years), male sex, coma, mental status disorder, thrombosis of the deep cerebral venous system, intracranial hemorrhage, malignancy, and central nervous system infection. About 30% of patients with one or more of these risk factors had a poor outcome despite treatment with heparin. For these patients endovascular thrombolysis might give better results.

Endovascular thrombolysis dissolves the thrombus by infusion of a thrombolytic drug into the occluded sinuses. It is often combined with mechanical techniques, such as thrombus disruption, thrombectomy with a rheolytic catheter, and thrombus removal with a balloon catheter.\(^6\) The theoretical advantage of thrombolysis for CVST is that the drug is delivered where needed, and downstream from cerebral venous—often hemorrhagic—infarcts. Mechanical methods result in more rapid recanalization and increase the surface of the thrombus exposed to thrombolytics. We treated 20 patients with severe CVST with endovascular thrombolysis in a prospective study, analyzed the results, and compared them with results of previous studies.

Methods
We selected patients with cerebral sinus thrombosis with an assumed poor prognosis because of an altered mental status (cognitive...
Table 1. Baseline Clinical Data of 20 Patients With CVST, Treated With Thrombolysis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Cause or Risk Factor</th>
<th>Start to Diagnosis (days)</th>
<th>Diagnosis to Heparin (days)</th>
<th>Heparin to Thrombolysis (days)</th>
<th>GCS 1</th>
<th>GCS 2</th>
<th>Pupils (right/left)</th>
<th>Risk Factors</th>
<th>Outcome (Rankin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M 36</td>
<td>M</td>
<td>36</td>
<td>ALL; L-asp. ++</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>7</td>
<td>+/+</td>
<td>++</td>
<td>1,2,5,6 death</td>
</tr>
<tr>
<td>2 M 29</td>
<td>M</td>
<td>29</td>
<td>hyperthyroidy +</td>
<td>12</td>
<td>0</td>
<td>14</td>
<td>14</td>
<td>+/+</td>
<td>TC</td>
<td></td>
<td>4,5,6 0</td>
</tr>
<tr>
<td>3 F 19</td>
<td>F</td>
<td>19</td>
<td>OAC</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>13</td>
<td>+/+</td>
<td></td>
<td>3,4 0</td>
</tr>
<tr>
<td>4 M 12</td>
<td>M</td>
<td>12</td>
<td>head injury -</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>+/+</td>
<td>TC</td>
<td>2,3,5 0</td>
</tr>
<tr>
<td>5 F 27</td>
<td>F</td>
<td>27</td>
<td>ALL ++</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>--</td>
<td>--</td>
<td>1,2,3,6 death</td>
</tr>
<tr>
<td>6 F 36</td>
<td>F</td>
<td>36</td>
<td>OAC ++</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>15</td>
<td>10</td>
<td>+/+</td>
<td>TC</td>
<td>4,6 0</td>
</tr>
<tr>
<td>7 F 40</td>
<td>F</td>
<td>40</td>
<td>ALL; L-asp. ++</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>+/+</td>
<td>TC</td>
<td>1,4,6 2</td>
</tr>
<tr>
<td>8 F 40</td>
<td>F</td>
<td>40</td>
<td>-- ++</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>+/+</td>
<td>TC</td>
<td>2,6 1</td>
</tr>
<tr>
<td>9 F 19</td>
<td>F</td>
<td>19</td>
<td>OAC</td>
<td>6</td>
<td>0</td>
<td>11</td>
<td>10</td>
<td>+/+</td>
<td>--</td>
<td>TC</td>
<td>3,4 3</td>
</tr>
<tr>
<td>10 M 57</td>
<td>M</td>
<td>57</td>
<td>+</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>+/+</td>
<td>TC</td>
<td>2,5,6 2</td>
</tr>
<tr>
<td>11 F 25</td>
<td>F</td>
<td>25</td>
<td>OAC</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>+/+</td>
<td>TC</td>
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<td>12 F 41</td>
<td>F</td>
<td>41</td>
<td>severe anemia --</td>
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<td>9</td>
<td>15</td>
<td>8</td>
<td>+/+</td>
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<td>2,3 1</td>
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<tr>
<td>13 F 23</td>
<td>F</td>
<td>23</td>
<td>myeloprolif. disorder, OAC</td>
<td>27</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>+/+</td>
<td>--</td>
<td>2,3,6 2</td>
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<tr>
<td>14 F 17</td>
<td>F</td>
<td>17</td>
<td>head injury +</td>
<td>5</td>
<td>0</td>
<td>15</td>
<td>7</td>
<td>+/+</td>
<td>+/+</td>
<td>TC</td>
<td>2,3,6 2</td>
</tr>
<tr>
<td>15 F 39</td>
<td>F</td>
<td>39</td>
<td>post partum +</td>
<td>2</td>
<td>0</td>
<td>coma</td>
<td>4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2,6 0</td>
</tr>
<tr>
<td>16 F 25</td>
<td>F</td>
<td>25</td>
<td>ulcerative colitis +</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>coma</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>2,6 0</td>
</tr>
<tr>
<td>17 F 31</td>
<td>F</td>
<td>31</td>
<td>OAC ++</td>
<td>5</td>
<td>0</td>
<td>10</td>
<td>9</td>
<td>+/+</td>
<td>--</td>
<td>--</td>
<td>3,4,6 death</td>
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<tr>
<td>18 F 43</td>
<td>F</td>
<td>43</td>
<td>-- +</td>
<td>3</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>+/+</td>
<td>F</td>
<td>3,4,6</td>
<td>1</td>
</tr>
<tr>
<td>19 F 46</td>
<td>F</td>
<td>46</td>
<td>--</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>+/+</td>
<td>--</td>
<td>2,3,4</td>
<td>0</td>
</tr>
<tr>
<td>20 F 38</td>
<td>F</td>
<td>38</td>
<td>OAC</td>
<td>3</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>+/+</td>
<td>--</td>
<td>--</td>
<td>3,4 0</td>
</tr>
</tbody>
</table>

ALL indicates acute lymphatic leukaemia; L-asp, L-asparaginase; OAC, oral anti-conceptive; H, Haemorrhagic infarct on base-line CT or MRI scan (+ minor, ++ large); GCS 1, at or shortly before diagnosis; GCS 2, at or shortly before endovascular treatment; TC, tonic clonic seizure; F, focal seizures.

Risk factors for a poor outcome as found in the ISCVT: 1, malignancy; 2, coma; 3, deep venous system thrombosis; 4, mental status disorder; 5, male sex; 6, hemorrhagic infarct.

Results

We treated 20 patients (16 women, 4 men) with a mean age of 32 years (range 12 to 57). Most patients (17/20) were referred from other hospitals because of worsening CVST. Details are given in Table 1. The median delay between onset of symptoms and diagnosis was 3.5 days. The mean Glasgow coma score (GCS) was 7.6 (range 3 to 14). Twelve patients were comatose before treatment. Fourteen patients had hemorrhagic infarcts before thrombolysis. Eleven patients had thrombosis of the deep cerebral venous system. Ten patients had generalized tonic-clonic seizures, with an epileptic status in one. Three patients had acute lymphatic leukemia (ALL; treated with L-asparaginase in 2). For radiological and treatment data see supplemental Table I, available online at http://stroke.ahajournals.org.

All patients were treated with heparin (conventional or full dose LMW) at the day of the diagnosis or the next day, except for 1 in whom heparin was delayed 5 days because the referring clinicians considered it contraindicated because of a large hemorrhagic infarct (case 6). Two patients (8 and 12) deteriorated and became comatose during treatment with heparin and improved after thrombolysis. In 15 patients we applied thrombolysis and thrombectomy, in 4 thrombolysis only. In 1 case (patient 19) it was impossible to enter the sinuses because of firm organized thrombus.
Nine patients recovered or had minimal residual symptoms (Rankin 0 or 1), 3 came out with a minor handicap (Rankin 2), 2 had a moderate or severe handicap (Rankin 3 and 4), and 6 died. Patients who died more frequently had leukemia (3/6) and large hemorrhagic infarcts (4/6) as compared to survivors (0/14 and 2/14, respectively; \( P=0.02 \) and 0.04). Seizures occurred less frequently in the fatal cases (1/6) than in the surviving patients (10/14; \( P=0.05 \)). Patients who died had a larger mean lesion size than the survivors (30.5 versus 13.6 cm\(^2\); \( P=0.03 \)), larger mean midline shift (5.2 versus 1.7 mm; \( P=0.02 \)), and a shorter delay between onset and diagnosis than those who survived (2.7 versus 8.2 days; \( P=0.01 \)). Other potential risk factors (age, coma, straight sinus thrombosis) were not associated with a fatal outcome.

Death was caused by transtentorial herniation in all patients, confirmed by autopsy in one. Five patients who died were already in early or advanced stages of herniation before thrombolysis, consistent with their large unilateral infarcts with midline shift (patients 1, 5, 7), large bilateral lesions (patients 15 and 16), obliterated basal cisterns, and fixed and dilated pupils (one unilaterally, three bilaterally), all before thrombolysis. Patients 15 and 16 were in a very bad clinical condition, and thrombolysis was performed as a last therapeutic option with very little hope for recovery. Four of the patients who died (5, 7, 15, 17) had an increased amount of intraventricular or parenchymal blood on the CT scan after thrombolysis. Patient 17 had a relatively small left temporal hemorrhagic infarct, which became larger and more hemorrhagic after thrombolysis and caused fatal herniation. In one surviving patient (14) thrombolysis was followed by a hemorrhagic infarct and a large local hemorrhage in the neck from the jugular puncture. She recovered with minor residual symptoms.

### Discussion

Twelve patients had excellent recovery or minor handicaps. Eight had a poor outcome, of whom 6 patients died despite maximally supportive treatment. A number of factors contributed to the poor results in these patients. The most conspicuous feature of the patients who died was their significantly larger midline shift, caused by large unilateral hemorrhagic infarcts, or the presence of large bilateral lesions at baseline, all causing herniation. This agrees with a previous study, which showed that the most frequent cause of early death in CVST is cerebral herniation.\(^{14}\) The delay between onset and diagnosis was 2.7 days for the patients who died, significantly shorter than for the survivors, which is compatible with a rapid deterioration attributable to early large hemorrhagic infarcts. The fact that 5 patients had mildly (3) or evidently (2) increased cerebral hemorrhage after thrombolysis, of whom 4 died, indicates that the procedure might be unacceptably hazardous in some cases. The number of increased hemorrhages in our series is larger than in previous studies. This may be related to the higher number of pretreatment hemorrhagic infarcts in our patients (Table 2). Nevertheless, we believe that in only 1 of these cases (patient 17) the increased hemorrhage may have contributed to the fatal outcome. The other patients were already in a very serious condition before thrombolysis.

### Table 2. Comparison of Previously Published Case Series, a Review of Cases Reports, and the Present Study of Thrombolysis for CVST

<table>
<thead>
<tr>
<th></th>
<th>Previous Case Series(^{1–10})</th>
<th>Cases Reviewed up to 2001(^{11})</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>82</td>
<td>142</td>
<td>20</td>
</tr>
<tr>
<td>Coma</td>
<td>4%</td>
<td>32%</td>
<td>60%</td>
</tr>
<tr>
<td>Baseline hemorrhagic infarcts</td>
<td>18%</td>
<td>33%</td>
<td>70%</td>
</tr>
<tr>
<td>New or increased cerebral hemorrhage</td>
<td>7%</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>Death</td>
<td>5%</td>
<td>9%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Three patients who died suffered from ALL. Sinus thrombosis is a well known complication of ALL.\(^{15,16}\) The combination of ALL and sinus thrombosis has a worse prognosis than each condition separately.\(^{16}\) Factors that contribute to poor outcome are effects of chemotherapy (L-asparaginase) and thrombocytopenia. Two patients with ALL (5 and 7) had some increased intraventricular blood on their CT scan after thrombolysis and low thrombocyte counts of 131 and 43×10\(^3\)/L, respectively. Remarkably, the surviving patients more often had seizures than the patients who died. A possible explanation is that patients with multiple seizures in acute sinus thrombosis can be severely ill with impaired consciousness between seizures, even in the absence of severe infarcts or hemorrhages. The presence of seizures may have caused recruitment of some patients with small cerebral lesions and a good prognosis despite their impaired consciousness, in whom standard treatment with heparin and antiepileptics might have been sufficient for a good outcome.

The first case reports of thrombolysis for CVST were published around 1990, initially by neurosurgeons who introduced a catheter via a burr hole into the superior sagittal sinus or applied open thrombectomy, followed by reports of endovascular treatment. A systematic review of all published cases of thrombolysis for CVST up to July 2001 identified 146 patients in 72 publications of single case reports or uncontrolled case series.\(^{13}\) Six larger series have been published,\(^^{7–12}\) the largest containing 20 patients.\(^{11}\) Some baseline data and results from these studies are compared with our study in Table 2. This shows that the outcomes of endovascular treatment probably depend strongly on case mix. The best results were obtained in the 6 case series, in patients with the best baseline conditions, followed by the cases reviewed by Canha. In comparison, in our study more patients were comatose; they more often had hemorrhagic infarcts before treatment, and had the highest death rate.

The main rationale for endovascular thrombolysis is earlier recanalization of the sinuses. In 2 of our patients this seems to have reversed a relentless deterioration in spite of heparin. However, thrombosed cortical veins are probably not opened by thrombolysis of the sinuses. Also, thrombolysis apparently comes too late for patients with impending herniation. Based on this experience, we changed our policy to hemispherectomy for such patients. Some promising results have been reported.\(^{17,18}\)

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In conclusion, our results of endovascular treatment for severe CVST are less favorable than the results of earlier studies, which may be explained in part by publication bias and differences in case mix. A randomized clinical trial to compare endovascular treatment with standard treatment (heparin) in selected patients is needed, but will be difficult to realize in this rare condition.

Disclosures
None.

References
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