Local Intra-Arterial Thrombolysis in Acute Ischemic Stroke

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Background and Purpose—We performed a retrospective analysis of the prognostic factors in patients treated with local intra-arterial thrombolysis (LIT). The purpose of this study was to evaluate the safety and efficacy of LIT using urokinase in patients with acute ischemic stroke of the anterior or posterior circulation and to determine the influence of clinical and radiological parameters on outcome.

Methods—Forty-three patients were treated with LIT using urokinase (median dose, 0.75×10⁶ IU). The median National Institutes of Health Stroke Scale (NIHSS) score at hospital admission was 18 (range, 9 to 36). Nine patients had occlusions of the internal carotid artery (ICA), 23 of the middle cerebral artery (MCA), 1 of the anterior cerebral artery, and 10 of the basilar artery (BA). Outcome was assessed after 3 months and classified as good for Rankin Scale (RS) scores of 0 to 3 and poor for RS scores of 4 or 5 and death.

Results—Nine patients (21%) recovered to RS scores 0 or 1, 17 (40%) to scores of 2 or 3, and 7 (16%) to scores of 4 or 5. Ten patients (23%) died. Outcome was good in 17 patients (80%) with MCA occlusions, in 3 patients (33%) with ICA, and in 5 patients (50%) with BA occlusions. Good outcome was associated with an initial NIHSS score of <20 (P<0.001), improvement by 4 or more points on NIHSS score within 24 hours (P=0.001), and vessel recanalization (P=0.02). Recanalization was more likely if LIT was started within 4 hours (P=0.01). Symptomatic cerebral hemorrhage occurred in 2 patients (4.7%).

Conclusions—LIT was most efficacious in patients with MCA and BA occlusions when the initial NIHSS score was less than 20 and when treated within 4 hours. It is of limited value in patients with distal ICA occlusions. (Stroke. 1998;29:1894-1900.)

Key Words: angiography, digital subtraction ■ fibrinolysis ■ stroke, acute ■ thrombolysis ■ urokinase

Thrombolysis using intravenous recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke is encouraging since it increased the number of patients with good functional outcome in the National Institute of Neurological Disorders and Stroke (NINDS) trial, and the recently published PROACT trial may renew the interest in local intra-arterial thrombolysis (LIT) because it enhances the arterial recanalization rate. Intravenous thrombolysis has been criticized as being a “shotgun approach” because it ignores specificity. However, there are no randomized trials comparing intravenous thrombolysis with LIT. Only a few reports from uncontrolled trials have suggested that LIT may be more efficacious than intravenous thrombolysis.

The purpose of this study was to evaluate the safety and efficacy of LIT using urokinase in patients with acute ischemic stroke of the anterior or posterior circulation and to determine the influence of clinical and radiological parameters on outcome.

Subjects and Methods

From December 1992 to July 1, 1997, 43 patients (19 women, 24 men; mean±SD age, 52.9±14.5 years; range, 12.7 to 74.6 years) with acute ischemic stroke were treated with LIT in our hospital. Patients were treated if (1) clinical diagnosis was established by a staff neurologist; (2) CT excluded intracranial hemorrhage or other nonvascular anomaly; (3) digital subtraction angiography demonstrated a vascular pathology explaining the neurological deficit; (4) the delay from symptom onset to LIT therapy was less than 6 hours or substantial worsening of stroke signs had occurred within the last 4 hours; (5) their age was less than 75 years; and (6) there were no individual contraindications or laboratory anomalies advising against the use of thrombolytics.

Clinical assessment was performed at admission, 24 hours after LIT, and before discharge using the National Institutes of Health Stroke Scale (NIHSS). Primary neuroradiological assessment was performed with CT in 42 patients and with MRI in 1. Selective intra-arterial digital subtraction angiography was performed on a biplane, high-resolution angiography system (Toshiba CAS 500, Tokyo, Japan) with a matrix of 1024×1024 pixels. A 5.5 F-JB2 (Valavanis, Cook, Denmark) catheter was used via the femoral approach for diagnostic cerebral panangiography in each patient to visualize the collateral flow and the occluded vessel.

LIT was performed according to clinical, CT, and angiographic findings and after information and consent of the patient and his/her family. At least 2 members of the stroke team, a neurologist and neuroradiologist, decided on its indication in the angiography suite. Using a microcatheter, mostly a Fast Tracker (Target Therapeutics)

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through the 5.5 F-JB2 catheter, which was navigated into the occluded vessel using biplane road map technique, a median dose of 750,000 IU urokinase (Urokinase HS Medac) (range, 20,000 to 1,250,000 IU) was infused either directly into or near the proximal end of the thrombus over 60 minutes. In 7 patients with atherosclerotic stenoses at the intracranial occlusion site and 1 patient with a stenosis at the internal carotid artery (ICA) origin, the stenoses were additionally dilated by percutaneous transluminal angioplasty (PTA), using a stealth PTA balloon catheter (Target Therapeutics). Treatment effect after thrombolysis was documented by a nonselective control arteriogram (see Tables 3 and 4), performed in identical biplane projections as the initial diagnostic angiogram before thrombolysis. Immediately after LIT, 27 patients received heparin in a dose doubling the activated thromboplastin time. After publication of the International Stroke Trial results, heparin was replaced by aspirin.8 Aspirin was given to 16 patients.

Occlusions were categorized as seen on angiograms before LIT. Collaterals were classified in 2 groups: none/minimal, if none or minimal intracranial or leptomeningeal anastomoses were present and therefore no sufficient filling of the territory distal to the occlusion was visible; and moderate/maximal, if moderate or maximal filling of extracranial, intracranial (circle of Willis), or leptomeningeal anastomoses with sufficient filling of the postocclusion vascular territory was seen.

The achieved vessel recanalization was classified as described by Mori and coworkers9: grade 0, unchanged; grade 1, movement of thrombus not associated with any improvement in perfusion; grade 2, partial recanalization with perfusion in less than 50% of the ischemic area; grade 3, partial recanalization with reperfusion in more than 50% of the ischemic area; or grade 4, complete or nearly complete recanalization with full return of perfusion. The threshold of 50% was taken in the later analysis of low (<50%) and high (>50%) grades of recanalization.9

Neurological improvement (NI) at 24 hours was defined as improvement of 4 or more points on the NIHSS. Either CT or high-field MRI were repeated within 3 days after LIT.

The etiology of stroke was determined after the acute phase with the help of additional investigations as deemed necessary in each

### TABLE 1. Clinical and Neuroradiological Baseline Characteristics, Type of Occlusion, and Outcome of 43 Patients Treated With LIT

<table>
<thead>
<tr>
<th></th>
<th>Distal ICA</th>
<th>MCA</th>
<th>BA</th>
<th>ACA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>NIHSS &lt;14</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15–19</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>≥20</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Time delay to LIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 hours</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>&gt;4 hours</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMCAS present</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>HMCAS absent</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Collaterals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal/none</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Moderate/maximal</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Recanalization &lt;50%</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>NI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>6</td>
<td>17</td>
<td>6</td>
<td>26</td>
</tr>
</tbody>
</table>

Good outcome is defined as RS 0–3 and poor outcome as RS 4 or 5, or death (RS 6).
patient. It was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Outcome assessment was carried out by a clinical examination 3 months after LIT using the modified Rankin scale (RS), which is known to have a high interobserver agreement: RS scores of 0 to 3 were defined as “good” and scores of 4 or 5 and death (RS 6) as “poor” outcomes. Also, to compare our results with those from the NINDS study, the outcomes were grouped into 4 categories: RS scores of 0 to 3 as “good”, scores of 4 or 5 and death (RS 6) as “poor” outcomes. Also, to compare our results with those from the NINDS study, the outcomes were grouped into 4 categories: RS scores of 0 to 3 as “good”, scores of 4 or 5 and death (RS 6) as “poor” outcomes.

### Results

The clinical and neuroradiological baseline characteristics and outcome categories are shown in Table 1 for each type of occlusion. The occlusion sites were as follows: ICA in 9 patients (21%); 6 of them with carotid “T” occlusions), middle cerebral artery (MCA) in 23 patients (53%; M1 segment in 17 [40%]; M2-4 segments in 6 [13%]), anterior cerebral artery in 1 patient (2.3%), and basilar artery (BA) in 10 patients (23%).

### Etiology

Large-artery atherosclerosis was present in 10 patients (23%), cardioembolism in 19 (44%), stroke of other determined etiology in 4 (9%), and stroke of undetermined etiology in 10 (23%). There was no lacunar infarction due to small-vessel occlusion. Twelve patients (28%) had had previous cerebrovascular events and 39 (91%) had vascular risk factors.

### Outcome

Twenty-six patients (60%) had a good and 17 (40%) a poor outcome. In detail, 9 patients (21%) recovered to RS score of 0 or 1, 17 (40%) retained a mild disability (RS 2 or 3), 7 (16%) remained severely disabled (RS 4 or 5), and 10 (23%) died.

### National Institute of Health Stroke Scale Score at Admission and Outcome

The median stroke severity measured at admission was 18 (range, 9 to 36). Twenty-three of 27 patients (85%) with NIHSS score of <20 at admission experienced a good outcome. In contrast, only 3 of 16 patients (19%) with a score of ≥20 had a good outcome. Eight of the 10 deaths occurred in this subset. The severity of stroke measured as NIHSS score at admission had a statistically significant influence on the outcome ($\chi^2 = 20.0, df = 2, P < 0.001$; Table 2).

### Delay to Treatment and Outcome

The median delay from symptom onset to LIT was 285 minutes (range, 130 to 840 minutes). Sixteen patients (35%) were treated within 4 hours and 36 patients (84%) within 6 hours. Twelve of the 16 patients (75%) treated within 4 hours had a good outcome. Twenty-seven patients (65%) were treated after 4 hours, 14 (52%) had a good outcome and 13 (48%) a poor outcome. The data show a trend toward a more favorable outcome in patients treated within 4 hours, but this trend was not significant ($\chi^2 = 1.8, df = 1, P = 0.17$).

### Vessel Recanalization and Outcome

The occluded vessel was recanalized successfully in 27 patients. This corresponds to a recanalization rate of 63%. Twenty of these 27 patients (74%) had a good outcome. In contrast, only 6 of 16 patients (38%), in whom recanalization was not achieved, did well. Successful recanalization was significantly associated with a good outcome ($\chi^2 = 5.62, df = 1, P = 0.018$; Table 3).

### Delay to Treatment and Vessel Recanalization

Fourteen of 15 patients (93%) treated within 4 hours had recanalizations >50%. Patients treated after 4 hours showed a slight preponderance of poor recanalization <50% (15 versus 13 patients). The delay to LIT had a significant effect on the recanalization rate ($\chi^2 = 9.2, df = 2, P = 0.01$; Table 4).

### Neurological Improvement Within 24 Hours and Outcome

Eleven patients had an NI. All improved to a good outcome. The NI was strongly associated with a good outcome ($\chi^2 = 9.7, df = 1, P = 0.002$; Table 5).

### TABLE 2. Stroke Severity (NIHSSS) at Admission and Outcome as Assessed 3 Months After LIT

<table>
<thead>
<tr>
<th>NIHSSS</th>
<th>Good (RS 0–3)</th>
<th>Poor (RS 4–6)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤14</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>15–19</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>≥20</td>
<td>3</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>17</td>
<td>43</td>
</tr>
</tbody>
</table>

$\chi^2 = 5.62, df = 1, P = 0.018$.

### TABLE 3. Vessel Recanalization After LIT as Seen on the Control Arteriogram and Outcome as Assessed After 3 Months

<table>
<thead>
<tr>
<th>Recanalization Grade</th>
<th>Good (RS 0–3)</th>
<th>Poor (RS 4–6)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>20</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>17</td>
<td>43</td>
</tr>
</tbody>
</table>

<50% indicates Mori recanalization grades 0–2; >50%, Mori recanalization grades 3–4.

$\chi^2 = 10.5, df = 2, P = 0.005$. 
Collaterals, Recanalization, and Outcome

Collaterals were moderate or maximal in 21 patients. In 16 (76%) recanalization was achieved. Twenty-two patients had minimal or no collaterals. Recanalization was successful in only 11 patients (50%). There was no association between collaterals and recanalization or between collaterals and outcome.

Hemorrhage

Asymptomatic hemorrhage was detected in 6 patients (14%) examined with MRI. All hemorrhages, mostly cortical, were in the ischemic brain parenchyma. Symptomatic intraparenchymal hemorrhage occurred in 2 patients (4.7%) with MCA M1 occlusions, a 61-year-old man and a 68-year-old woman. The man had a NIHSS score of 12 and recovered to a slight disability (RS score of 2). The woman had a NIHSS score of 21 and died due to transtentorial herniation 4 days after LIT.

Deaths

Ten patients died (23%), 6 due to progressing edema and transtentorial herniation and 4 due to a brain stem stroke. Eight had an NIHSS score of ≥20 at admission. Collaterals were minimal or absent in 8 and recanalization was <50% in 6 patients.

Occlusions in the Anterior Circulation

Nine patients had occlusions of the ICA, 6 of them carotid T occlusions. Outcome was good in 3 (33%; all T occlusions) and poor in 6 (67%). Two patients died. Five patients (56%) had severe neurological deficits of NIHSS score ≥20 at admission. Four of them had a poor outcome. The recanalization rate (33%) was lower than in the other patients.

Twenty-three patients suffered occlusions of the MCA. Seventeen patients (74%) had a good outcome. Patients with MCA occlusions had better outcomes than those with ICA occlusions (χ²=4.5, df=1, P=0.03; Table 6). Recanalization was achieved in 13 of 17 patients (76%) with good outcomes and in 2 of 6 (30%) with poor outcomes (χ²=3.63, df=1, P=0.056). Collaterals were not different in the 2 outcome groups. The MCA main stem (M1 segment) was occluded with lenticulostriate arteries in 14 patients (61%). Eight of them (57%) had a good outcome, 3 a poor outcome, and 3 died. In 3 patients the occlusion of M1 was distal to the lenticulostriate arteries, and in 6 only MCA branches were occluded (Table 7). They all had a good outcome. There was a nonsignificant trend toward better outcomes with more distal MCA occlusions (χ²=5.2, df=2, P=0.074).

The NIHSS score was less than 20 in 18 patients and associated with a good outcome in 16 patients (89%). As in distal ICA occlusions, 4 of 5 patients with severe MCA strokes with an NIHSS score of ≥20 on admission had a poor outcome. However, the relative number of patients with such severe strokes (5/23, 22%) was lower than in the group with ICA occlusions (5/9, 56%).

The presence of the hyperdense MCA sign (HMCAS) was analyzed for the 32 patients with ICA or MCA occlusion. Twenty-six patients had angiographically proven occlusions of the M1 segment. Twenty-three of them (88%) showed a HMCAS. No patient with a patent M1 segment showed a positive HMCAS. Accordingly, in the 6 patients with occlusions of the M2–M4 segments, the HMCAS was absent. The 23 patients with HMCAS had a median NIHSS score of 19 (range, 11 to 24) on admission. This value was not different from the median NIHSS score of 17 (range, 9 to 21) of the 9 patients without HMCAS. Ten of 12 patients (83%) with a poor (83%) and 13 of 20 (65%) with a good outcome had a positive HMCAS (χ²=1.24, df=1, P=0.26). Furthermore, there was no significant correlation between HMCAS and recanalization.

A 70-year-old man suffered an anterior cerebral artery occlusion. His initial NIHSS score was 10 at admission. Recanalization was achieved within 3 hours. He recovered to RS 3.

Occlusions of the BA

Ten patients suffered from BA occlusion. Five had a good outcome. Four patients with NIHSS score <20 on admission had a good outcome, whereas 5 of 6 patients with severe strokes (NIHSS ≥20) had a poor outcome. There was no association of good outcome to early treatment within 4 hours from symptom onset. Three patients were treated after 6 hours. Two of them had a poor outcome. Collaterals did not

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**TABLE 5. Neurological Improvement of 4 or More Points on NIHSS 24 Hours After LIT and Outcome 3 Months Later**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Good (RS 0–3)</th>
<th>Poor (RS 4–6)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>15</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>17</td>
<td>43</td>
</tr>
</tbody>
</table>

χ²=9.7, df=1, P=0.002.

**TABLE 6. Comparison of ICA and MCA Occlusions and Outcome After 3 Months**

<table>
<thead>
<tr>
<th>Occlusion Site</th>
<th>Good (RS 0–3)</th>
<th>Poor (RS 4–6)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>MCA</td>
<td>17</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>12</td>
<td>32</td>
</tr>
</tbody>
</table>

χ²=4.5, df=1, P=0.033.

**TABLE 7. Occlusion Site in the MCA and Outcome After 3 Months**

<table>
<thead>
<tr>
<th>MCA Occlusion Site</th>
<th>Good (RS 0–3)</th>
<th>Poor (RS 4–6)</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>M1+ perforators</td>
<td>8</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>M1, patent perforators</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>M2–3</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

χ²=5.22, df=2, P=0.074.
affect the outcome. Recanalization >50% was achieved in 8 patients (80%), 5 of them (62.5%) had a good outcome. Asymptomatic hemorrhage occurred in 1 patient.

Four patients (40%) died due to strokes in the BA territory. Two of them were comatose at admission. Three of them had an atherosclerotic etiology of the occlusion and died despite the fact that recanalization was achieved.

Discussion

In this series of 43 stroke patients treated with LIT, 60% had a good and 40% a poor outcome. Outcome was significantly related to severity of stroke measured as NIHSS score at admission, vessel recanalization, NI within 24 hours, and location of vessel occlusion in the anterior circulation. Delay to treatment had an indirect effect on outcome, but collaterals as seen on angiograms, HMCAS, and etiology of stroke did not influence it.

The NIHSS score is a measure of the severity of stroke. Our patients with an NIHSS score of ≥20 at admission had a worse prognosis than patients with a score of <20. A correlation between severity of stroke and outcome has been observed in other stroke trials as well. A large infarct is associated with a high NIHSS score and has a worse prognosis than a small stroke with a low NIHSS score. In the NINDS trial, lacunar strokes had the best prognosis. Patients whose occluded vessels recanalized had a better prognosis than patients whose vessels did not. This corroborates findings of other studies in which intra-arterial or intravenous thrombolysis was used, where recanalization was also associated with a better prognosis. The recanalization rate for all of our patients was 63%, for patients with distal ICA occlusions 33%, and for those with MCA occlusions 86% to 92%. In a meta-analysis, 64%, range 40% to 100%, in a meta-analysis, 56%. These figures are similar to other intra-arterial thrombolysis studies (64%, range 40% to 100%, in a meta-analysis). In acute MCA strokes Bollaert and coworkers obtained 58% MCA recanalizations with recombinant pro-urokinase and proved its superiority to placebo. Delay to treatment has been identified as an additional factor for success of intravenous thrombolysis. In our patients, delay to treatment did not have a directly measurable effect on outcome. This may be because of our small sample. However, the earlier treatment was begun, the more likely the occluded vessel was to recanalize; because recanalization was associated with a better prognosis, earlier treatment may have favored a good outcome indirectly.

NI within 24 hours has been shown to be an additional criterion associated with a favorable outcome. It occurred in 26% of our patients and was significantly related to a good outcome. It possibly reflects the effect of recanalization restoring neuronal function in the penumbra.

HMCAS on initial CT had no prognostic value in our patients. This is in line with other stroke trials that showed no correlation or only a poor correlation between HMCAS and outcome, whether patients were treated or not. Conversely, Tomsick and coworkers observed mostly poor clinical outcomes in a series of patients treated within 90 minutes with intravenous rtPA when HMCAS was present. However, in their study, the median baseline NIHSS score of HMCAS-positive patients was 19.5 compared with 10 with HMCAS-negative patients, and this may have accounted for the different clinical outcome in their patients. In our series, HMCAS-positive and -negative patients had an NIHSS score in the same order. Von Kummer et al found that the HMCAS per se was of low prognostic value. However, it predicted a fatal outcome if extended hypodensity or brain swelling was seen in addition to the HMCAS on CT, ie, when extensive brain damage had already occurred. There was no correlation between HMCAS and recanalization in our patients or in another series, which further underscores the low prognostic value of HMCAS.

The site of occlusion plays a key role in the outcome of stroke. In the anterior circulation, patients with carotid occlusions were characterized by severe neurological deficits, poor recanalization rates, and worse outcomes than those with MCA occlusions. However, our patients with carotid occlusions did not fare as badly as the patients studied by Zeumer et al. Zeumer and coworkers reported a fatal outcome in 59% and persistent severe neurological deficits in 38% of patients with carotid occlusions. The recanalization of 17% was low. In comparison, 3 of our 9 carotid occlusion patients’ vessels recanalized and they had a good outcome. Therefore, we still think that LIT in carotid occlusions is worth attempting and that it has the potential to spare some patients a large stroke.

Patients with BA thrombosis have a poor prognosis when recanalization does not occur. In large series, mortality was 86% to 92%. LIT enhances the recanalization rate, gives the patient with recanalization a fair chance of favorable outcome, and reduces mortality significantly. Five of our 8 patients (63%) who recanalized had a good and 2 who did not had a poor outcome. However, 2 who were comatose at admission died despite successful recanalization. Our data on BA occlusions are in line with larger series and support the opinion that LIT should be attempted in noncomatose patients with BA occlusion.

Symptomatic hemorrhages occurred in 4.7% of our patients. One of them (2.3%) bled 3 days after LIT while under heparin, which may have caused the hemorrhage. The spontaneous bleeding rates were 1.2% in NINDS and 6.5% in European Cooperative Acute Stroke Study (ECASS) control groups. A meta-analysis showed spontaneous rates of 2.6% and 9.6% with intravenous thrombolysis. Our 4.7% are in the same range or only slightly elevated compared with the spontaneous course, but higher than the 0.7% reported by Théron and coworkers in 142 patients.

It seems that intra-arterial thrombolysis carries a smaller risk of bleeding than intravenous thrombolysis, but to date direct comparisons of intra-arterial and intravenous thrombolysis have not been done.

Recanalization rates, which relate to outcome, were higher after intra-arterial application of the fibrinolytics than in a study with intravenous administration of rtPA (63% versus 29%).
In the placebo-controlled NINDS study, 157 patients were treated within 90 minutes and 155 within 180 minutes. In our study the median delay to treatment was 285 minutes. The median NIHSS score at admission in NINDS was 14 (range, 1 to 36) and in the present series 18 (range, 9 to 36). Mean age in NINDS was 69±12 years, 16 years greater than in the present series. “Small vessel occlusive” strokes were included in NINDS, in the present series they were not. In summary, compared with NINDS, patients in this series suffered more severe strokes, treatment was started later, and only patients with angiographically confirmed vessel occlusions were treated. Only the younger age favored our patients. All these differences limit a comparison. If, nonetheless, outcomes are compared, our LIT patients had the same ratio of good versus poor outcomes as in NINDS part 2 subset (LIT, 1.53 to 1; NINDS, 1.5 to 1).

According to indirect comparisons of intravenous and intra-arterial thrombolysis, a cautious statement would be that LIT is at least as effective and safe as intravenous thrombolysis with rtPA and it can be applied with a longer time window. In addition, LIT has several advantages. Angiography performed before LIT visualizes the individual vascular pathology; it gives information on collateral flow; the thrombolytic agent can be applied into the thrombus under visual control; the fibrinolytic dose needed for vessel recanalization is smaller than in systemic thrombolysis; sometimes the thrombus can be fragmented and dislodged mechanically; and PTA can be performed through the same guiding catheter. The risk of symptomatic intracranial hemorrhage does not seem to increase or at least not as much as in systemic thrombolysis.

Limitations of LIT are that it can be delivered only at large institutions with an interventional neuroradiological service. Some angiograms will be performed in vain, eg, when spontaneous recanalization takes place before angiography, when stroke is due to microangiopathy, or when an ICA occlusion prevents LIT of an occluded MCA.

It is our impression that patients with occlusions of large cerebral arteries such as the ICA, MCA main stem, or the BA gain most from LIT, whereas patients with branch occlusions are served as well with intravenous treatment. However, to corroborate such a statement a direct comparison of intra-arterial and intravenous thrombolysis would be necessary.

In conclusion, the present study indicates that LIT with urokinase in acute ischemic stroke is a safe treatment and that it achieves a high recanalization rate correlating with a good outcome, especially within the first 4 hours. It is less efficacious in comatose patients with BA occlusions and in patients with carotid T occlusions. An NIHSS score of ≥20 is an unfavorable sign as well.

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