Thrombolysis in Patients With Acute Stroke Caused by Cervical Artery Dissection

Analysis of 9 Patients and Review of the Literature

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Background: Results of recently published studies suggest that intravenous thrombolysis (IVT) and local intra-arterial thrombolysis (LIT) are feasible procedures in acute stroke after cervical artery dissection (CAD).

Objectives: To describe 9 patients with acute stroke caused by CAD who were treated by LIT (n=7) or IVT (n=2) and to review the literature.

Methods: Retrospective analysis of clinical and neuroradiological findings; literature review from 1980 to present.

Main Outcome Measure: Modified Rankin Scale (mRS) score.

Results: Of 7 patients treated with LIT, 3 had good outcomes (mRS score of 0-2) and 4 had bad outcomes (mRS score of 3-6) at 3 months. The 2 patients who had received IVT recovered to mRS scores of 0 and 3. Twenty-one patients were identified in the literature. Overall (N=30), in the IVT group (n=19), the outcome was good in 8 patients (42%) and bad in 11 (58%); in the LIT group (n=11), 6 patients (55%) had a good outcome and 5 (45%) had a bad outcome. Overall, 47% (14/30) of the patients (IVT and LIT groups) had a good outcome. Total mortality was 13% (4/30). There were no secondary complications due to extension of wall hematoma or angiography. One symptomatic hemorrhage occurred.

Conclusions: Thrombolysis is feasible in acute stroke caused by CAD. Local complications from extension of wall hematoma did not occur. Further prospective studies are needed to determine the safety and efficacy of thrombolysis in the special circumstance of acute stroke caused by CAD.

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Original Contribution

From the Departments of Neurology (Drs Arnold, Nedeltchev, Sturzenegger, Schroth, Loher, Stepper, Bassetti, and Mattle) and Neuroradiology (Dr Remonda), University of Berne, Berne, Switzerland.

Cervical artery dissection (CAD) is a common cause of stroke in young patients. Recently, several authors published reports on single cases or small series of patients that suggest that intravenous thrombolysis (IVT) or local intra-arterial thrombolysis (LIT) can be performed in patients with acute stroke after CAD with limited or no procedure-related morbidity. We describe an additional 9 patients with CAD treated with thrombolysis and review the published literature on this therapeutic approach.

Results

Demographic, clinical, and individual outcome data are summarized in Table 1 and Table 2. The Figure shows angiographic results from patient 3 in our study. In the LIT group (n=7), 4 patients with stenotic vertebral artery dissection had occlusions of the basilar artery, and 2 patients with stenotic and occlusive cervical internal carotid artery dissection had occlusions of the M1 segment of the middle cerebral artery. Posttreatment angiograms showed complete recanalization of the intracranial artery (Thrombolysis in Myocardial Infarction grade 3) in 1 of 7 patients and partial recanalization (grade 2) in 2 of 7. No changes in the dissected extracranial cerebral arteries were observed in posttreatment angiograms. There were no angiographic complications related to the dissection.

In the 2 patients with internal carotid artery occlusions treated with IVT, no posttreatment angiograms were performed. Of 7 patients in our study treated with LIT, 3 had good outcomes (mRS score of 0-2) and 4 had bad outcomes (mRS score of 3-6) at 3 months. In 2 patients in our study who underwent IVT, the individual 3-month mRS scores were 0 and 3. There were no recurrent strokes during 3-month follow-up in our 9 patients. Of 21 patients described in the literature, 17...
PATIENTS AND METHODS

Between December 1, 1992, and January 1, 2001, 169 patients with acute ischemic stroke were treated at the University of Berne with local intra-arterial urokinase (n=163) or intravenous recombinant tissue plasminogen activator (n=6). Inclusion and exclusion criteria have been published previously.6

Local intra-arterial thrombolysis was performed if (1) a clinical diagnosis of ischemic stroke was established by a neurologist; (2) baseline National Institutes of Health Stroke Scale score reached at least 4 points (except for isolated hemianopia or aphasia); (3) computed tomographic scanning excluded intracranial hemorrhage; (4) 4-vessel cerebral angiogram showed an intracranial vessel occlusion correlating with the neurological deficit; (5) the expected interval from symptom onset to LIT was less than 6 hours for carotid territory stroke and less than 12 hours for basilar artery occlusion; and (6) there were no individual clinical or laboratory findings advising against thrombolysis. Intra-arterial urokinase was administered directly into the occluded intracranial arteries distal to the dissection. Recanalization on posttreatment angiogram was graded according to Thrombolysis in Myocardial Infarction trial criteria.9

Intravenous thrombolysis was performed if cervical vessel occlusion precluded access to the target intracranial vessel and only if the procedure could be done within 3 hours of stroke onset, as provided by the National Institute of Neurological Disorders and Stroke IVT protocol. Clinical assessment was performed at hospital admission using the National Institutes of Health Stroke Scale.10

Of 169 patients treated with thrombolysis, 9 had angiographically identified dissections before thrombolysis—5 in a single carotid artery, 2 in a single vertebral artery, and 2 in both vertebral arteries. The 2 patients with unilateral vertebral artery dissections reported minor neck traumas preceding the stroke. In the others, no potential cause could be identified. The 7 LIT patients were treated with urokinase (mean dose, 590000 IU; range, 400000 to 1 million IU). Treatment effect was documented by arteriography immediately after thrombolysis. Two patients with internal carotid artery occlusion from dissection received intravenous recombinant tissue plasminogen activator (0.9-mg/kg body weight). After thrombolytic therapy, 7 patients were treated with heparin in a dose doubling the activated thromboplastin time and 2 were given aspirin daily (250 mg).

Control computed tomography or magnetic resonance imaging was performed within 24 hours of thrombolysis. Duplex sonograms were obtained within 12 to 48 hours of thrombolysis to evaluate the status of the dissected artery. Outcome was assessed by clinical neurological evaluation 3 months after thrombolysis using the modified Rankin Scale (mRS).11 Modified Rankin Scale scores of 0 to 2 were defined as “good” outcomes, and scores of 3 to 6 were defined as “bad” outcomes.

The following complications were considered to be potentially related to thrombolysis: symptomatic intracerebral hemorrhage, systemic hemorrhage, and subarachnoid hemorrhage. Lower cranial nerve palsy, Horner syndrome occurring or progressing after thrombolysis, and clinical deterioration after thrombolysis suggestive of secondary vessel occlusion or extension of the dissection were considered to be local complications of thrombolysis.

Review of the English, German, and French literature on CAD and its treatment with thrombolysis included all publications from 1980 to the present found in MEDLINE or quoted in articles. Twenty-one additional patients were identified.12-17 Treatment methods, types and rates of complications, and outcome data were sufficiently well documented to allow us to analyze these patients in a single pool with our 9 patients. In 4 studies in which the mRS score was not given, we interpolated a score based on reported clinical findings. However, systemic hemorrhage rates were not reported in 2 of the 3 literature sources,14,15 and details regarding recurrent strokes were not routinely available. Therefore, we restricted these 2 analyses to the 9 patients from our experience.

underwent IVT and 4 underwent LIT. After IVT, outcome was good in 7 patients and bad in 10. After LIT, 3 patients had good outcomes and 1 died.

Overall (study and literature patients), in the IVT group (n=19), the outcome was good in 8 patients (42%) and bad in 11 (58%); in the LIT group (n=11), 6 patients (55%) had good outcomes and 5 (45%) had bad outcomes. Overall, 47% (14/30) of the patients had good outcomes. Mortality was 13% (4/30).

Only 1 patient reported in the literature experienced a symptomatic intracerebral hemorrhage 36 hours after intravenous recombinant tissue plasminogen activator therapy. Thus, the rate of symptomatic intracerebral hemorrhage was 3% (1/30). One patient in our study (11%) experienced an intracranial hematoma at the site of the arterial puncture. Data on systemic hemorrhage are not given for the patients described in the literature.7

In neither our series nor the patients described by other researchers were secondary local complications related to thrombolysis observed. No angiographic complications related to the dissection were reported.

Thrombolysis is an accepted therapy for acute ischemic stroke.12,17 When it comes to acute stroke caused by CAD, the experience with thrombolysis is limited. Mostly, the stroke physician sees patients with CAD before they experience an ischemic deficit, or patients present late, that is, when the time window for thrombolysis has elapsed. In such situations, heparin is considered as optimal treatment to prevent first or recurrent stroke, although use of heparin has never been supported by a randomized trial.14,15,18 Anticoagulants in such situations can abolish microemboli detected by transcranial Doppler sonography, and patients with CAD and microemboli are at higher risk for recurrent stroke than are those with CAD but without microemboli.17,18,19

The optimal treatment for the patient with CAD who presents within the time window when IVT or LIT are therapeutic options has never been studied. The question arises whether thrombolysis of the embolus lodged in the intracranial vessel is beneficial to and safe for the patient. There

COMMENT


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is a danger that thrombolysis may extend the wall hematoma in the dissected artery and may cause local complications or further hamper cerebral circulation. In addition, there is the risk of intracranial hemorrhage after thrombolysis, as occurs in other patients with stroke.19

In our small series of 9 patients and in 21 patients described in the literature who received IVT or LIT for acute stroke caused by CAD, only 1 patient (3%) experienced a symptomatic intracranial hemorrhage. Therefore, the risk of intracranial hemorrhage does not seem to be increased compared with other patients with stroke.

In addition, none of the 30 patients experienced a symptomatic local complication of the dissected vessel because of thrombolysis. Because routine cervical magnetic resonance imaging before and after thrombolysis has not been performed systematically, asymptomatic extension of a wall hematoma or asymptomatic progressive vessel narrowing cannot be ruled out. However, the absence of

Table 1. Demographic and Clinical Outcome Data for 9 Study Patients With Cervical Artery Dissection Treated by Thrombolysis*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Delay, min</th>
<th>Therapy</th>
<th>Radiological Findings After Thrombolysis</th>
<th>Dissected Arteries, Side</th>
<th>Baseline NIHSS Score</th>
<th>3-mo Outcome mRS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/40</td>
<td>80</td>
<td>IA urokinase</td>
<td>Bilateral cerebellar and left occipital infarction</td>
<td>VA, L, R</td>
<td>18</td>
<td>1</td>
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<td>2/F/48</td>
<td>175</td>
<td>IA urokinase</td>
<td>L basal ganglia infarction</td>
<td>ICA, L</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>3/M/40</td>
<td>250</td>
<td>IA urokinase</td>
<td>L anterior MCA infarction</td>
<td>ICA, L</td>
<td>22</td>
<td>3</td>
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<td>4/M/68</td>
<td>210</td>
<td>IA urokinase</td>
<td>L dorsolateral medullar and basal ganglia infarction</td>
<td>VA, L</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>5/F/43</td>
<td>385</td>
<td>IA urokinase</td>
<td>Bilateral pontine and cerebellar infarction</td>
<td>VA, L</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>6/M/43</td>
<td>285</td>
<td>IA urokinase</td>
<td>L bilateral pontine infarction</td>
<td>VA, L</td>
<td>33</td>
<td>5</td>
</tr>
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<td>7/M/52</td>
<td>225</td>
<td>IA urokinase</td>
<td>L total MCA infarction</td>
<td>ICA, L</td>
<td>19</td>
<td>4</td>
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<tr>
<td>8/F/42</td>
<td>135</td>
<td>IV rt-PA</td>
<td>R basal ganglia infarction</td>
<td>ICA, R</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>9/F/57</td>
<td>155</td>
<td>IV rt-PA</td>
<td>R basal ganglia and insular infarction</td>
<td>ICA, R</td>
<td>18</td>
<td>0</td>
</tr>
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</table>

*Delay indicates interval from cerebral symptoms to thrombolysis; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IA, intra-arterial; VA, vertebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; IV, intravenous; rt-PA, recombinant tissue plasminogen activator.

is a danger that thrombolysis may extend the wall hematoma in the dissected artery and may cause local complications or further hamper cerebral circulation. In addition, there is the risk of intracranial hemorrhage after thrombolysis, as occurs in other patients with stroke.19

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Table 2. Demographic and Clinical Outcome Data for 21 Literature Review Patients With Cervical Artery Dissection Treated by Thrombolysis*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient No./Sex/Age, y</th>
<th>Delay, min</th>
<th>Therapy</th>
<th>Radiological Findings After Thrombolysis</th>
<th>Dissected Arteries, Side</th>
<th>Baseline NIHSS Score or Clinical Deficit</th>
<th>3-mo Outcome mRS Score</th>
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</thead>
<tbody>
<tr>
<td>Rudolf et al., 1999</td>
<td>1/M/54</td>
<td>105</td>
<td>IV rt-PA</td>
<td>L lacunar putaminal infarction</td>
<td>ICA, L</td>
<td>16</td>
<td>0</td>
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<tr>
<td></td>
<td>2/M/59</td>
<td>115</td>
<td>IV rt-PA</td>
<td>L lacunar capsular infarction</td>
<td>ICA, L</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3/F/59</td>
<td>120</td>
<td>IV rt-PA</td>
<td>L MCA and PCA infarction</td>
<td>ICA, L</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4/M/54</td>
<td>175</td>
<td>IV rt-PA</td>
<td>Subtotal R MCA infarction</td>
<td>ICA, L</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5/M/57</td>
<td>180</td>
<td>IV rt-PA</td>
<td>Anterior L MCA infarction</td>
<td>ICA, L</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Derex et al., 2000</td>
<td>6/M/60</td>
<td>&gt;180</td>
<td>IV rt-PA</td>
<td>L MCA, bilateral ACA infarction</td>
<td>ICA, I</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7/M/60</td>
<td>270</td>
<td>IV rt-PA</td>
<td>Global R MCA hypodensity</td>
<td>ICA, R</td>
<td>L hemiplegia, aphasia</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>8/M/48</td>
<td>390</td>
<td>IV rt-PA</td>
<td>Global R MCA hypodensity</td>
<td>ICA, R</td>
<td>L hemiplegia, aphasia</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>9/M/47</td>
<td>180</td>
<td>IV rt-PA</td>
<td>Global R MCA hypodensity, partial R ACA hypodensity</td>
<td>ICA, R</td>
<td>L hemiplegia, aphasia</td>
<td>NA</td>
</tr>
<tr>
<td>Sampognaro et al., 1999</td>
<td>5/M/56</td>
<td>195</td>
<td>IV rt-PA</td>
<td>L frontal ICH, deep L MCA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia, L Horner sign</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>6/M/51</td>
<td>210</td>
<td>IV rt-PA</td>
<td>Global L MCA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>7/M/54</td>
<td>220</td>
<td>IV rt-PA</td>
<td>Global L MCA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia</td>
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<td></td>
<td>8/M/56</td>
<td>420</td>
<td>IV rt-PA</td>
<td>Deep L MCA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia</td>
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<tr>
<td></td>
<td>9/M/56</td>
<td>310</td>
<td>IV rt-PA</td>
<td>Global R MCA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia</td>
<td>NA</td>
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<td></td>
<td>10/M/56</td>
<td>225</td>
<td>IV rt-PA</td>
<td>Deep L MCA, hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, aphasia</td>
<td>NA</td>
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<td></td>
<td>11/F/27</td>
<td>210</td>
<td>IV rt-PA</td>
<td>Global R MCA hypodensity, partial R ACA hypodensity</td>
<td>ICA, L</td>
<td>R hemiplegia, R Horner sign</td>
<td>NA</td>
</tr>
<tr>
<td>Ahmad et al., 1999</td>
<td>1/M/38</td>
<td>&gt;180</td>
<td>IA UK</td>
<td>L basal ganglia infarction, L corona radiata infarction</td>
<td>ICA, L</td>
<td>R hemiplegia</td>
<td>1</td>
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<td>Price et al., 1998</td>
<td>1/M/33</td>
<td>Not available</td>
<td>IA rt-PA</td>
<td>Not available</td>
<td>VA, R</td>
<td>Coma, R hemiparesis, fixed dilated left pupil</td>
<td>1</td>
</tr>
</tbody>
</table>

*Delay indicates interval from cerebral symptoms to thrombolysis; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IA, intra-arterial; VA, vertebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; IV, intravenous; rt-PA, recombinant tissue plasminogen activator.
symptoms or signs indicating such events suggests that the dissected vessel is not damaged further by thrombolytic therapy.

Local intra-arterial thrombolysis involves the general risks of angiography and an additional risk of fragmentation of a thrombus with displacement of parts of it to the distal intracranial circulation. In addition, the arteriographic catheter might be placed into the false, rather than the true, lumen of the dissected vessel and perforate it. Such complications did not occur in 11 patients treated by LIT.

Because of the small number of patients, the heterogeneity of patients, and the lack of a control group in our study, it is not possible to address the efficacy of thrombolysis in patients with acute stroke and dissection. Overall, 14 (47%) of 30 patients undergoing LIT and IVT had good outcomes. Thirteen (43%) of these 30 patients had excellent outcomes (mRS score of 0 or 1). Total mortality was 13% (4/30). Although the patients in this series had mostly severe infarcts, our outcome results are similar to those for the National Institute of Neurological Disorders and Stroke part 2 subset patients,12
of whom 39% treated with intravenous recombinant tissue plasminogen activator had an excellent outcome and 17% died. The outcome data are also comparable to the results of the intra-arterial Prolyse in Acute Cerebral Thromboembolism II trial, in which 40% of the patients treated with recombinant prourokinase had a good outcome (mRS score of 0-2) and mortality was 25%. Several publications on CAD point to a good outcome in most patients, even when there are focal cerebral ischemic events. But the outcome depends on the severity of the initial ischemic deficit. For example, in a series by Bogousslavsky et al, only 12 (40%) of 30 patients had a good outcome, and 7 patients (23%) died. The 9 patients in our study had moderate to severe strokes, with a median National Institutes of Health Stroke Scale score at hospital admission of 18, and the baseline clinical neurological deficits in the 21 patients with dissection and thrombolysis from the literature were also mostly moderate to severe. This can partly be explained by the fact that, in general, younger patients and patients with a severe clinical deficit are transferred urgently to a stroke unit, whereas hospital admission of patients with less severe deficits is frequently delayed and beyond the time window for thrombolysis.

In conclusion, the results of our study and a review of the literature that includes 21 patients indicate that thrombolysis in CAD involves similar risks as in other types of stroke. Special or additional risks such as local complications were not observed. The observations of the use of thrombolysis in acute stroke caused by CAD are encouraging. Further observational studies are needed to determine whether thrombolysis is really safe in this setting. It is unlikely that randomized trials will ever be performed in patients with this condition. However, indirect comparisons of larger series of patients with CAD vs patients with stroke from other causes might provide an answer regarding efficacy. In addition, the question of whether IVT or LIT is more beneficial to such patients must be resolved as well.

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Author contributions: Study concept and design (Drs Arnold, Nedeltchev, Sturzenegger, Schroth, Loher, and Mattle); acquisition of data (Drs Arnold, Nedeltchev, Loher, Stepper, Remonda, Bassetti, and Mattle); analysis and interpretation of data (Drs Arnold, Sturzenegger, Schroth, Bassetti, and Mattle); drafting of the manuscript (Drs Arnold, Nedeltchev, Loher, Stepper, and Mattle); critical revision of the manuscript for important intellectual content (Drs Arnold, Sturzenegger, Schroth, Remonda, Bassetti, and Mattle); statistical expertise (Dr Arnold); obtained funding (Dr Mattle); administrative, technical, and material support (Drs Arnold, Sturzenegger, Schroth, and Mattle); study supervision (Drs Sturzenegger, Schroth, Bassetti, and Mattle).

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REFERENCES