Early Intravenous Thrombolysis With Recombinant Tissue-type Plasminogen Activator in Vertebrobasilar Ischemic Stroke

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Background: The optimal therapy of vertebrobasilar ischemic stroke is under debate. In the case of underlying basilar artery occlusion, intra-arterial thrombolysis is recommended. Because this pathologic condition is rarely found and the procedure is time consuming and restricted to specialized centers, the question arises whether early intravenous thrombolysis could also effectively be applied in vertebrobasilar ischemic stroke.

Objective: To determine if early intravenous thrombolysis could be used effectively in vertebrobasilar ischemic stroke.

Design: A case series of 12 consecutive patients with acute vertebrobasilar ischemia were followed up 3 months after thrombolytic treatment at the Department of Neurology of the University Hospital of Cologne, Cologne, Germany, a primary care and referral center.

Methods: Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous recombinant tissue-type plasminogen activator within 3 hours after symptom onset following a protocol similar to that of the National Institute of Neurological Disorders and Stroke study.

Results: On admission, 7 patients exhibited moderate to severe brainstem symptoms without impairment of consciousness and 5 patients had impairment of consciousness, of whom 2 were comatose. Of 12 patients, 10 had a favorable outcome after 3 months defined as full independence (Barthel index score of 100) or return to pre-morbid condition. One patient had a poor outcome with complete dependency due to reocclusion after primarily successful thrombolysis, and 1 patient died of severe brainstem infarction and additional space occupying parietal hemorrhage.

Conclusion: Favorable outcome could be achieved in the majority of 12 consecutive patients with moderate to severe vertebrobasilar ischemic stroke treated with intravenous recombinant tissue-type plasminogen activator within 3 hours after symptom onset.

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VERTEBROBASILAR ischemic stroke accounts for about 20% of all ischemic strokes. An unfavorable outcome (major or fatal stroke) is found in as many as 60% of patients. In cases of basilar artery occlusion, mortality can be as high as 90%. Despite its poor prognosis, the optimal therapy of vertebrobasilar ischemic stroke remains undetermined.

Angiography and, in cases of basilar occlusion, subsequent intra-arterial thrombolysis is considered the optimal management for vertebrobasilar ischemic stroke. However, intra-arterial thrombolysis is restricted to a few highly specialized centers only, and the procedure is time consuming. The time between onset of symptoms and the beginning of thrombolytic therapy is a crucial factor in the success of thrombolytic therapy. From the National Institute of Neurological Disorders and Stroke (NINDS) study we learned that intravenous thrombolysis can be used safely and effectively within 3 hours after symptom onset. Therefore, should patients with acute vertebrobasilar ischemia admitted to a hospital without angiography facilities within 3 hours after symptom onset be treated immediately with intravenous thrombolysis or transported to respective centers for intra-arterial thrombolysis?

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PATIENTS AND METHODS

Between March 1996 and July 1997, we treated 93 consecutive patients with acute ischemic stroke with intravenous rtPA within 3 hours after symptom onset; of these, 12 patients had vertebrobasilar ischemic strokes.

The diagnosis of vertebrobasilar ischemic stroke was based on the presence of typical brainstem symptoms (eg, cranial nerve palsies, dysarthria, dysphagia, ataxia, pareses, and impairment of consciousness). Occlusion of the basilar artery was not documented before treatment.

Inclusion and exclusion criteria were adopted from the NINDS study. Patients were not included if the onset of symptoms could not be defined precisely and witnessed or if the patients had pure vertigo or isolated cranial nerve palsy.

On admission, neurologic deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a 42-point scale that quantifies neurologic deficit. Normal function without neurologic deficit is scored as zero, while complete hemiplegia with aphasia, gaze deviation, visual deficit, dysarthria, and sensory loss is given a score of 25, for example. Outcome at 3 months was determined using the NIHSS, Barthel index, and Rankin scale. The Barthel index (0-100) is a measure of the ability to perform activities of daily living such as eating, bathing, walking, and using the toilet. Patients able to perform all activities with complete independence are given a score of 100. The Rankin scale (0-5) is a simplified overall assessment of function in which a score of 0 indicates the absence of symptoms and a score of 5 indicates severe disability. To compare our results, patients were classified according to the criteria of the NINDS study. A score of 1 or less using the NIHSS criteria, 95 to 100 using the Barthel index, and 0 to 1 using the Rankin scale indicated no or minimal functional deficit. A score of 2 to 8 using the NIHSS criteria, 55 to 90 using the Barthel index, and 2 to 3 using the Rankin scale indicated mild or moderate functional deficit. A score of 9 or higher using the NIHSS criteria, 0 to 50 using the Barthel index, and 4 to 5 using the Rankin scale indicated severe functional deficit. “Favorable outcome” was defined as full independence (Barthel index of 100) or return to premorbid condition.

After obtaining informed consent from the patient or next of kin, 0.9 mg/kg of rtPA (alteplase [Actilyse, Thomae, Biberach, Germany]) was administered intravenously during a 60-minute period (10% bolus and 90% continuously). For early prevention of recurrent thrombosis and analogous to coronary thrombolysis, anticoagulation with heparin was routinely performed immediately after the end of rtPA infusion, aiming to increase activated partial thromboplastin time to 1½ to 2 times the standard normal values.

Unenhanced computed tomographic (CT) scanning of the head was routinely performed on admission, 24 hours after admission, and whenever neurologic deterioration occurred. In some patients, follow-up magnetic resonance imaging, magnetic resonance angiography, or CT angiography was performed. Although transcranial Doppler ultrasonography was not routinely performed before treatment, it was performed within the first 24 hours.

Classification of stroke was based on the information available at discharge.

RESULTS

Twelve patients (9 men and 3 women) with typical, progressive brainstem symptoms were treated (Table). The mean (± SD) age was 63 ± 10 years (range, 41-78 years); the mean (± SD) interval between symptom onset and thrombolytic treatment was 134 ± 26 minutes (range, 100-175 minutes); and the mean (± SD) initial NIHSS score was 14 ± 11 points, with a median NIHSS score of 12 points (range, 4-37 points). Five patients had impairment of consciousness and hemiparesis or tetraparesis or decerebrate posturing, and 2 of these patients were comatose. In 6 patients, brainstem involvement could be demonstrated in the results of follow-up CT or magnetic resonance imaging.

In 1 patient (patient 10), basilar artery occlusion was documented in the results of transcranial Doppler ultrasonography before treatment.

Atherothrombosis was the most frequent cause (6 patients), and embolism was less frequent (2 patients). In 1 patient (patient 7), dissection of the vertebral artery was documented in the results of CT angiography; in 3 patients, the cause remained undetermined. Excellent outcome with no or minimal functional deficit was reached in 7 patients. Of the 7, 4 patients had severe brainstem symptoms with impairment of consciousness on admission (patients 7, 8, 9, and 10); in 2 patients, brainstem infarction could be assessed in the results of follow-up magnetic resonance imaging. In 2 more patients (patients 1 and 2), the outcome was good with a score of 100 using the Barthel index, 2 using the Rankin scale, and mild neurologic sequelae (4 and 2 points, respectively, using the NIHSS criteria). In these patients, brainstem infarction was also documented. One patient (patient 4) showed considerable improvement: Neurologic deficit was minimal after 3 months (NIHSS, 1 point); however, the activities of daily living and grade of dependency were moderately impaired but comparable to the premorbid condition.

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Taken together, a favorable outcome was reached in 10 of 12 consecutive patients.

In the remaining 2 patients (patients 11 and 12), the outcome was poor. A 65-year-old patient (patient 11) experienced a sudden onset of left-sided hemiparesis, followed by nausea and progressive loss of consciousness. On arrival at our hospital 90 minutes after symptom onset, he was comatose with decerebrate posturing. The results of cranial CT demonstrated a hyperdense basilar artery. Intravenous thrombolysis with 80 mg of rtPA was initiated 120 minutes after onset of symptoms; thrombolysis was effective. After 24 hours, his neurologic status was normal except for a moderate dysarthria. Three
Vertebrobasilar ischemic stroke is different in many ways from stroke in the carotid axis. It is less frequent, its prognosis is worse, and atherosclerosis is the most frequent cause. Therefore, the transfer of therapeutic concepts from hemispheric to vertebrobasilar ischemic stroke is limited. Therapeutic trials especially designed for vertebrobasilar ischemic stroke are rare and mostly restricted to patients with angiography-proved basilar artery occlusion, although this pathologic characteristic is only found in about 14% of patients with vertebrobasilar ischemic stroke. The main therapeutic strategy tested is local intra-arterial thrombolysis. Even after successful recanalization, an approximate mortality rate of 50% has been reported. However, there are also occasional reports of benign outcome in angiography-proved basilar artery occlusion without thrombolytic therapy. The length of basilar artery obstruction, the state of the collaterals, and the clinical condition on admission were valuable prognostic factors. To our knowledge, no randomized, placebo-controlled trial of thrombolytic therapy in acute basilar artery occlusion has been conducted. The only larger studies conducted were those of Hacke and coworkers in 1988, Brandt and coworkers in 1996, and Zeumer and coworkers in 1993. Almost all patients were treated with intra-arterial thrombolysis within various time frames, some of them even later than 24 hours after symptom onset. However, intra-arterial thrombolysis is restricted to a few specialized centers that have angiography facilities and special teams available 24 hours a day. Furthermore, intra-arterial thrombolysis is a time-consuming procedure with a long “door-to-needle” time. As experimental data show, the duration of ischemia is a crucial factor for the success of therapeutic intervention. Furthermore, the symptoms of vertebrobasilar ischemic stroke are often fluctuating or progres-

### Comment

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### Clinical, Diagnostic, Treatment, and Outcome Data on the Patients

<table>
<thead>
<tr>
<th>Patient No./ Age, y/ Sex</th>
<th>Interval, min</th>
<th>Neurologic Findings on Admission</th>
<th>Results of Imaging Studies</th>
<th>Cause</th>
<th>Initial NIHSS</th>
<th>Scores Using NIHSS/ Barthel Index/Rankin Scale at 3 Months</th>
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<tbody>
<tr>
<td>1/74/M 125</td>
<td>Crossed brainstem syndrome</td>
<td>MRI: pontine infarction</td>
<td>Embolism</td>
<td>8</td>
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<tr>
<td>2/65/M 100</td>
<td>Hemiparesis, ataxia, dissociated sensory deficit</td>
<td>CT: pontine infarction; TCD: BA stenosis</td>
<td>Atherosclerosis</td>
<td>5</td>
<td>2/100/2</td>
<td></td>
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<tr>
<td>3/76/M 100</td>
<td>Dysphagia, dysarthria, paresis of abducens nerve, nuclear facial palsy</td>
<td>No infarct</td>
<td>Embolism</td>
<td>9</td>
<td>0/100/0</td>
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<tr>
<td>4/68/F 100</td>
<td>Vertigo, dysphagia, dysarthria, gaze palsy, facial paresis, bilateral Babinski sign</td>
<td>CT: pontine infarction; TCD: high-grade BA stenosis</td>
<td>Atherosclerosis</td>
<td>12</td>
<td>1/60/3</td>
<td></td>
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<tr>
<td>5/68/M 140</td>
<td>Vertigo, diplopia, nystagmus, nuclear facial palsy, dysarthria, paresis of nerve IX</td>
<td>No infarct</td>
<td>Atherosclerosis</td>
<td>4</td>
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<tr>
<td>6/57/F 160</td>
<td>Horner syndrome, hemiparesis, sensory deficit without facial involvement</td>
<td>No infarct</td>
<td>Undetermined</td>
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<tr>
<td>7/41/M 175</td>
<td>Impairment of consciousness and hemiparesis, dysarthria, nuclear facial palsy, paresis of abducens nerve</td>
<td>CT and CTA: lacunar thalamic infarction, vertebral artery dissection</td>
<td>Dissection</td>
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<tr>
<td>8/65/M 170</td>
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<td>MRI: brainstem infarction</td>
<td>Undetermined</td>
<td>16</td>
<td>1/100/1</td>
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<tr>
<td>9/53/M 135</td>
<td>Impairment of consciousness, dysarthria, internuclear opthalmoplegia, gaze palsy, tetraparesis, bilateral sensory deficit</td>
<td>MRI: brainstem infarction; MRA: BA stenosis</td>
<td>Atherosclerosis</td>
<td>14</td>
<td>0/100/0</td>
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<tr>
<td>10/49/F 120</td>
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<td>TCD: acute BA occlusion</td>
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<td>37</td>
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<tr>
<td>11/65/M 120</td>
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<td>TCD and MRA: high-grade BA stenosis</td>
<td>Atherosclerosis</td>
<td>36</td>
<td>17/55/4</td>
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<tr>
<td>12/70/M 160</td>
<td>Vertigo, dysarthria, severe hemiparesis</td>
<td>CT and CTA: brainstem infarction, hemorrhage, high-grade BA stenosis</td>
<td>Atherosclerosis</td>
<td>14</td>
<td>Died</td>
<td></td>
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</tbody>
</table>

*NIHSS indicates the National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; CT, computed tomography; TCD, transcranial Doppler ultrasonography; BA, basilar artery; CTA, computed tomographic angiography; and MRA, magnetic resonance angiography. The Rankin scale was developed by van Swieten et al.17*
sive, sometimes leading to sudden deterioration. The better the clinical condition is on admission, the better the prognosis after thrombolysis.\footnote{Turner TM, Garraway WM, Whisnant JP. The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. Stroke. 1984;15:790-794.} Therefore, should patients with acute symptoms of brainstem ischemia be treated immediately with intravenous rtPA within the 3-hour time frame as in the NINDS study\footnote{The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-1587.} or be transferred to specialized centers for intra-arterial thrombolysis?

Data on intravenous thrombolysis with rtPA in vertebrobasilar ischemic stroke are scarce. In a larger study, von Kummer and coworkers\footnote{von Kummer R, Forsting M, Sartor K, Hacke W. Intravenous recombinant tissue plasminogen activator (rt-PA): a randomized clinical trial in patients with acute vertebrobasilar occlusion. Cerebrovasc Dis. 1995;5:182-187.} described 5 patients with angiography-proved basilar artery occlusion treated within 6 hours after symptom onset with 70 mg of rtPA intravenously. Because 3 patients died of extended brainstem infarction, 1 patient remained “locked in,” and only 1 patient fully recovered, intravenous treatment was abandoned. Huemer and coworkers\footnote{Kamps I, Weiss J, Ringelstein EB. Repetitive Behandlung einer subtotalen vertebrobasila¨ren Stenose mit “tissue plasminogen activator” (tPA). Nervenarzt. 1992;63:755-780.} described 16 patients with acute occlusion of the basilar artery treated with intravenous rtPA within 6 hours after symptom onset. The results were more encouraging since recanalization was achieved in 10 patients for intra-arterial thrombolysis-proved basilar artery occlusion treated within 6 hours after symptom onset. The results were more encouraging since recanalization was achieved in 10 patients. Herderschée and coworkers\footnote{Herderschee D, Limburg M, Hijdra A, Koster PA. Recombinant tissue plasminogen activator in two patients with basilar artery occlusion. J Neurol Neurosurg Psychiatry. 1991;54:71-73.} described 2 patients with angiography-proved basilar artery occlusion treated with 100 mg of rtPA intravenously. One patient was successfully treated 130 minutes after symptom onset, and the other patient was treated after 6 hours and died from hemorrhagic infarction of the pons despite extensive collateralization. The difference in time interval was crucial; in our patient 11, treatment within 2 hours was effective whereas a second treatment, which was beyond the early time frame, was ineffective. Kamps and coworkers\footnote{Kamps I, Weiss J, Ringelstein EB. Repetitive Behandlung einer subtotalen vertebrobasila¨ren Stenose mit “tissue plasminogen activator” (tPA). Nervenarzt. 1992;63:755-780.} also described a patient with subtotal vertebrobasilar stenosis and rapidly progressive severe brainstem symptoms who was successfully treated twice within 1 week. However, a permanent therapeutic success could not be achieved.

Whether thrombolysis should be followed immediately by administration of heparin in patients with acute vertebrobasilar ischemic stroke is a question that cannot be answered from our limited data. On the one hand, there is a substantial risk of reocclusion after successful thrombolysis due to underlying atherosclerotic pathologic factors\footnote{Heiss WD, Rosner G. Functional recovery of cortical neurons as related to degree and duration of ischemia. Ann Neurol. 1983;14:294-301.} as demonstrated in our patient 11; on the other hand, the risk of severe hemorrhage as shown in our patient 12 might be increased. Our data of favorable 3-month outcome in 10 of 12 consecutive patients treated within 3 hours after onset of typical brainstem symptoms suggest effectiveness of this treatment within the given time frame. Beyond that time frame, no conclusions can be drawn.

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REFERENCES