Intra-arterial Thrombolytic Therapy Improves Outcome in Patients With Acute Vertebrobasilar Occlusive Disease

Werner Hacke, MD, Hermann Zeumer, MD, Andreas Ferbert, MD, Hartmut Brückmann, MD, and Gregory J. del Zoppo, MD

In this retrospective analysis we report our treatment experience in 65 consecutive patients with clinical signs of severe brainstem ischemia with angiographically demonstrated thrombotic vertebrobasilar artery occlusions who received either local intra-arterial thrombolytic therapy (urokinase or streptokinase) (43 patients) or conventional therapy (antiplatelet agents or anticoagulants) (22 patients). We analyzed the data with respect to cerebral artery occlusion patterns, posttreatment arterial recanalization, and the clinical categories of favorable/unfavorable outcome and survival/death. In subgroup analyses, recanalization in patients who received thrombolytic therapy correlated significantly with clinical outcome; in 19 of 43 patients, recanalization was demonstrated angiographically, while in 24 patients the occlusion persisted. All patients without recanalization died, but 14 of the 19 patients displaying recanalization survived ($p = 0.000007$), 10 with a favorable clinical outcome. Only three of the 22 patients who received conventional therapy survived, all with a moderate clinical deficit. When we compared the treatment groups, highly significant differences in both outcome quality ($p = 0.017$) and survival ($p = 0.0005$) were found to depend on establishing recanalization. Our data support the concept that technically successful thrombolysis of vertebrobasilar artery occlusions is associated with beneficial clinical outcome. 

The prognosis of most patients with acute multiterritorial, life-threatening brainstem syndromes and angiographically proven vertebrobasilar (VB) artery occlusions is poor. The term multiterritorial syndrome (or alternans plus syndrome) refers to clinical ischemic symptoms that are not limited to the distribution of a typical arterial branch, that is, functional defects extend beyond the well-known territorial infarctions in the VB artery territory. Coma, “locked-in” syndrome, multilevel ocular motor disturbances, and bilateral motor deficits represent involvement of more than one ventral perforating artery at different brainstem levels. Although no prospective, controlled data exist on the outcome of patients with acute VB artery thrombosis, Kubik and Adams have stated that death occurs from 2 days to 5 weeks after the event in the majority of patients. Of 20 patients with VB artery territory ischemia described by Archer and Horenstein, 6 died, leaving five survivors severely disabled. In contrast, several reports of basilar or VB artery occlusion in asymptomatic persons and in patients with minor brainstem symptoms (e.g., brainstem transient ischemic attacks [TIAs], VB insufficiency, or recent brainstem territorial infarction) have suggested a benign outcome in those conditions. No treatment of the conditions with either severe or benign outcome has been established by controlled studies, whereas uncontrolled studies have failed to enlist a sufficient number of patients to permit conclusions regarding therapy. It would appear that acute severe brainstem stroke
with angiographically proven VB artery occlusion has a poor prognosis, with a mortality rate of at least 75%.

With respect to the high mortality rate and the lack of proven therapy, we have studied the incidence of arterial recanalization and clinical outcome following local intra-arterial infusion of urokinase or streptokinase in acute VB artery territory occlusion in 43 patients compared with 22 patients receiving conventional therapy. Early case reports and preliminary surveys have reported arterial recanalization associated with favorable clinical outcome following infusion of the thrombolytic agents.9-10,23-27 The angiographic findings and the clinical description of the 65 patients suffering VB artery occlusion have been detailed elsewhere,28-29 and Ferbert and coworkers30 have described the corresponding electrophysiologic data. In this article, we address two pertinent questions: 1) did patients benefit clinically from the recanalization of an occluded vessel?, and 2) which angiographic and clinical constellations indicate successful thrombolytic therapy?

Subjects and Methods

We report the retrospectively studied outcome of 22 patients with VB artery thrombosis receiving conventional therapy (antiplatelet agents or anticoagulants, Group A) and the prospectively studied outcome of 43 patients with acute angiographically documented VB artery thrombosis receiving thrombolytic therapy (local intra-arterial infusion of urokinase or streptokinase, Group B). Group A patients were enlisted between June 1975 and December 1982, whereas Group B patients were recruited between January 1983 and May 1986.

The patient characteristics and clinical outcomes, described in detail elsewhere,28-30 are summarized in Tables 1 and 2. Patient history was often incomplete because many patients were severely debilitated, and we could not reliably compare ancillary clinical conditions, etiology, or associations with vascular disease.

Group A patients received either antiplatelet agents (500 mg/day acetylsalicylic acid, n = 4) or anticoagulants (low-dose [3 × 5,000 units] heparin n = 10, or full-dose [3,000–5,000 units bolus and 1,000 units/hr infusion] heparin followed by warfarin, n = 8).

To exclude patients with longer-existing ischemic deficits, thrombolytic therapy was not started (except in two patients) if the mandatory preangiographic computed tomogram (CT scan) showed hypodense areas in the brainstem or the cerebellum. Most (29 of 43) Group B patients were treated ≤24 hours after the onset of their symptoms, but only six of

<table>
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<tr>
<th>Table 1. Characteristics of Patients With Vertebrobasilar Artery Thrombosis</th>
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<tr>
<td><strong>Number</strong></td>
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<tr>
<td><strong>Age (yr)</strong></td>
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<tr>
<td><strong>Mean</strong></td>
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<tr>
<td><strong>Range</strong></td>
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<tr>
<td><strong>Sex (male/female)</strong></td>
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<tr>
<td><strong>Clinical characteristics</strong></td>
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<tr>
<td><strong>Initial course</strong></td>
</tr>
<tr>
<td><strong>Acute onset</strong></td>
</tr>
<tr>
<td><strong>Progressive</strong></td>
</tr>
<tr>
<td><strong>Ratio</strong></td>
</tr>
<tr>
<td><strong>Motor abnormalities</strong></td>
</tr>
<tr>
<td><strong>Nil</strong></td>
</tr>
<tr>
<td><strong>Hemiplegia</strong></td>
</tr>
<tr>
<td><strong>Tetraparesis</strong></td>
</tr>
<tr>
<td><strong>Tetraplegia</strong></td>
</tr>
<tr>
<td><strong>Level of consciousness</strong></td>
</tr>
<tr>
<td><strong>Awake</strong></td>
</tr>
<tr>
<td><strong>Somnolent</strong></td>
</tr>
<tr>
<td><strong>Stuporous</strong></td>
</tr>
<tr>
<td><strong>Comatose</strong></td>
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<tr>
<td><strong>Occlusion patterns</strong></td>
</tr>
<tr>
<td><strong>TOP</strong></td>
</tr>
<tr>
<td><strong>MID</strong></td>
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<tr>
<td><strong>CVB</strong></td>
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<tr>
<td><strong>MXD</strong></td>
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</table>

All patient-related information and categories are taken from raw data in Brückmann et al.,28 as described in text. Data from Patient 45 has been deleted. Group A, patients receiving conventional therapy (antiplatelet agents/anticoagulants); Group B, patients receiving thrombolytic therapy (urokinase/streptokinase) by local intra-arterial infusion; Subgroup B₁, Group B patients displaying arterial recanalization; Subgroup B₂, Group B patients displaying no arterial recanalization; TOP, top-of-the-basilar-artery or cephalad occlusion; MID, midbasilar artery occlusion; CVB, caudal vertebrobasilar occlusion; MXD, other mixed occlusion patterns.
the eight Group B patients with acute onset of symptoms (Table 1) were treated within the first 6 hours. Approval for the thrombolytic therapy protocol and the informed consent requirements were obtained from the Institutional Ethics Committee of the Klinikum Rheinisch-Westfälische Technische Hochschule, Aachen, FRG. All Group B patients (and/or their relatives) gave consent before we initiated thrombolytic therapy.

In general, Group B patients received either urokinase or streptokinase at 100,000 units/hr for up to 4 hours by intermittent or continuous infusion, although some patients received lower dose rates (e.g., 10,000 units/hr) for longer periods (12–48 hours). All infusions were conducted through a superselective catheter positioned as proximal as possible to the occlusion. Heparin (300 units/hr) was routinely infused through the catheter concurrent with the thrombolytic agent. Heparin was thereafter infused at 1,000 units/hr i.v. Hemodilution therapy with hydroxyethyl starch (21 ml/hr) was routinely given after completion of the thrombolytic agent infusion. The infusion techniques have been described.

For purposes of analysis, we divided Group B into Subgroup B1, patients displaying arterial recanalization (n = 19), and Subgroup B2, patients displaying no arterial recanalization (n = 24).

We classified clinical and neuroradiologic entrance and outcome events retrospectively for Group A and prospectively for Group B. The clinical findings of both groups are derived from the original data and clinical classifications in the report of Brückmann et al. One patient (Patient 45) described in that summary has been excluded from our current analysis as he did not present with an acute brainstem stroke.

We employed the clinical status at the time of admission to the hospital as described. Patients judged to be in extremely poor clinical condition on admission were those presenting in coma, independent of other findings, and those stuporous with a demonstrable hemiparesis/hemiplegia or tetraplegia.

Four clinical neurologic outcomes were defined: no/minimal neurologic deficit (V), moderate deficit (W), severe deficit and locked-in syndrome (Y), or death (Z) as described. For the purposes of analysis, these outcomes have been categorized as favorable (V + W) or unfavorable (Y + Z) relative to the clinical status on admission. Clinical outcome was also categorized as survival (V + W + Y) or death (Z) at the time of transfer or discharge.

We used the angiographic classification of VB artery thrombosis according to Archer and Horenstein, which distinguishes between top-of-the-basilar-artery or cephalad occlusion (TOP), mid-basilar artery occlusion (MID), and caudal VB artery occlusion (CVB). Angiographic patterns that did not fit into these classes have been labeled mixed (MXD) occlusions.

All angiograms were reviewed in an unblinded fashion. Initial studies of Group A patients were scored only for position of occlusion and degree of VB blood flow. Studies of Group B patients were scored for both position of occlusion and presence (complete or partial) or absence of arterial recanalization.

We compared the groups by means of a series of chi-square tests, analysis of variance, and the exact contingency table of independence test for two subsets.

### Results

Clinical and angiographic characteristics of the groups are presented in Table 1. In general, no significant differences with regard to age, sex, initial course of stroke (acute vs. progressive or stuttering onset), or motor abnormalities on admission were noted between Groups A and B. However, specific differences between Subgroups B1 and B2 were apparent. Patients in Subgroups B1 and B2 were significantly younger than those in Group A (p = 0.01). While no significant difference in initial course of stroke was discernible between Groups A and B ($\chi^2, p = 0.92$), there were more patients with acute onset in Subgroup B2 than B1 ($p = 0.04$).

A significant difference in the level of consciousness was evident between Groups A and B ($\chi^2, p = 0.02$), due in part to the greater number of awake patients receiving thrombolytic therapy. A major
contributor to this difference was the larger number of awake patients in Subgroup B₁ (n = 9) and the large number of comatose patients receiving conventional therapy (n = 11). This dichotomy undoubtedly reflects the increased number of patients recruited with a higher level of consciousness after a testable therapeutic approach (thrombolysis) became available. This bias also seems responsible for the significant difference in age between Groups A and B because of the increased number of younger patients with basilar artery occlusion referred from other hospitals.

Fifty-one of the 65 patients in Groups A and B had a discrete angiographic pattern of VB artery occlusion; the 14 remaining patients showed MXD patterns consisting of either very extensive occlusions of the entire basilar artery or multilevel stenoses or occlusions (Table 1). No difference among occlusion patterns was apparent between Groups A and B or among Group A and Subgroups B₁ and B₂ (χ², p = 0.68).

The CT data of Group B has been detailed by Brückmann and coworkers.²⁸ Serial CT studies were performed before angiography, 24 hours after thrombolytic therapy, at least once during the first 7 days following treatment, as well as after abrupt changes in the clinical status.

Recanalization rates varied according to occlusion pattern, but no significant difference in the distribution of occlusion pattern was evident between Subgroups B₁ and B₂ (Table 1). Indeed, no occlusion pattern was significantly associated with an increase in the recanalization rate.

Tables 2 and 3 detail the clinical outcome for patients in each treatment subgroup and their statistical analyses. Subgroup B₁ patients improved significantly with regard to neurologic residua and mortality compared with Group A or Subgroup B₂ patients.

Twenty-three of the 65 patients (Table 4) were judged to be in extremely poor clinical condition on admission. Because of the small number of patients, there was no significant difference in the number of such patients between Subgroup B₂ and Group A (p = 0.20) or between Subgroups B₁ and B₂ (p = 0.20). Only one of the nine patients in Group A and none of the 10 patients in Subgroup B₂ judged to be in extremely poor clinical condition on admission survived; in Subgroup B₁, two of four such patients survived.

Four of the 43 Group B patients demonstrated hemorrhagic transformations, two in Subgroup B₁ and two in Subgroup B₂. In one patient bleeding was detected during routine CT scanning 4 days after treatment and in three by means of additional CT studies following clinical deterioration; acute deterioration in the level of consciousness in two and severe vegetative dysregulation in one comatose patient contributed to the hemorrhagic transformation.

<table>
<thead>
<tr>
<th>Occlusion pattern</th>
<th>TOP</th>
<th>MID</th>
<th>CVB</th>
<th>MXD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>22</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup B₁</td>
<td>19</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup B₂</td>
<td>24</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Data are number of patients; survivors in parentheses. Group A, patients receiving conventional therapy (antiplatelet agents/anticoagulants); Subgroup B₁, patients receiving thrombolytic therapy (urokinase/streptokinase) by local intra-arterial infusion displaying arterial recanalization; Subgroup B₂, patients receiving thrombolytic therapy displaying no arterial recanalization. TOP, top-of-the-basilar-artery or cephalad occlusion; MID, midbasilar artery occlusion; CVB, caudal vertebrobasilar artery occlusion; MXD, other mixed occlusion patterns.

### Table 5. Hemorrhagic Transformation in Patients With Vertebrobasilar Artery Thrombosis Receiving Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Occlusion</th>
<th>T-O (hr)</th>
<th>Agent</th>
<th>Total dose (units x 10³)</th>
<th>Duration (hr)</th>
<th>Antithrombotic agent(s)</th>
<th>Hemorrhagic agent</th>
<th>Death due to intracranial hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup B₁ (recanalization)</td>
<td>19/47/F</td>
<td>TOP</td>
<td>U</td>
<td>13</td>
<td>860</td>
<td>+</td>
<td>Antiplatelet</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>21/66/F</td>
<td>MID</td>
<td>S</td>
<td>6</td>
<td>70</td>
<td>+</td>
<td>Antiplatelet</td>
<td>-</td>
</tr>
<tr>
<td>Subgroup B₂ (no recanalization)</td>
<td>30/54/M</td>
<td>MXD</td>
<td>U</td>
<td>17+</td>
<td>1280</td>
<td>+</td>
<td>Antiplatelet</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>37/59/F</td>
<td>MID</td>
<td>U</td>
<td>76</td>
<td>1620</td>
<td>+</td>
<td>Antiplatelet</td>
<td>-</td>
</tr>
</tbody>
</table>

Pt, patient number from Reference 28; T-O, interval from onset of symptoms to initiation of treatment with thrombolytic agent; heparin by continuous 500 units/hr infusion, duration variable; hemorrhagic agents, principally hydroxyethyl starch; F, female; M, male; TOP, top-of-the-basilar-artery or cephalad occlusion; MID, midbasilar artery occlusion; MXD, other mixed occlusion patterns; U, urokinase; S, streptokinase.
patient necessitated additional CT studies in these three patients. Pontine hemorrhage associated with a variable extension into cerebellar structures was shown in three patients; in one woman a slight hemorrhagic transformation was found. Serial laboratory tests including fibrinogen level, activated partial thromboplastin time, and fibrin split products did not show any particular changes different from those found in the majority of the patients. Hemorrhage was apparently responsible for death in two patients, one in each subgroup (Table 5). Three of the four patients had received urokinase in an extended infusion (8.6–16.2 × 10⁵ units total over 11–24 hours), and all patients had received heparin and a hemorrheologic agent. Ultimately, all patients who hemorrhaged died. One patient (Patient 37) with a massive parenchymatous hemorrhage received treatment 3.2 days after the onset of symptoms and displayed recanalization.

Discussion

The use of thrombolytic agents in patients with symptoms of acute severe cerebral or brainstem ischemia rests on the observation that a majority of acute strokes in the carotid and VB territories result from atherothrombotic or thromboembolic processes. The mechanism of action and the use of thrombolytic agents in cerebral arterial disease has recently been reviewed. Early studies of intravenous thrombolytic agents in nonacute stroke patients did not assess arterial recanalization or clinical outcome independent of the risk of intracerebral hemorrhage. A number of case reports published since 1980 have shown that arterial recanalization can be associated with clinical improvement following intra-arterial infusion of thrombolytic agents. Given the growing interest in the systemic use of thrombus-specific fibrinolytic agents such as tissue plasminogen activator (tPA) or single-chain urokinase plasminogen activator in acute stroke, we believe that it is useful to discuss the clinical outcome in our series of 43 patients with acute VB artery occlusion receiving local thrombolytic therapy. Since the outcome events of arterial recanalization and clinical improvement are theoretically in part interdependent, a favorable clinical outcome will be attributable to the thrombolytic therapy only if arterial recanalization is demonstrated.

The improvement in clinical outcome and survival in the Subgroup B patients was highly significant compared with Subgroup B patients and with Group A patients. While we found some subgroup differences, Groups A and B were comparable in all respects except level of consciousness and age. This difference seems to be caused by the increasing number of younger patients with basilar artery occlusion being referred from other hospitals once a possible treatment became available.

The potential outcome following local thrombolytic therapy may be influenced by the pathogenetic mechanisms of VB ischemia such as atherothrombotic stenoses and occlusions, in situ thrombosis or embolism, severity of initial symptoms, and the natural history of a particular occlusion pattern. The caudal vertebral arteries, VB junction, and midbasilar artery are common sites for significant atherosclerosis and in situ thrombosis. This might contribute to the low rate of recanalization (43%) we found, which is lower than the rates reported in studies of acute carotid artery territory occlusions and acute coronary artery thrombosis. However, we found no particular occlusion pattern preferentially associated with recanalization.

While no prospective angiographic studies in untreated basilar artery stroke patients have been performed to determine the expected spontaneous recanalization rate, clinical experience and analogy to middle cerebral artery embolism suggest that the spontaneous recanalization rate is higher in (cardiac-source) top-of-the-basilar embolism than in conditions associated with thrombus formation on preexisting atheromatous stenoses or occlusions (midbasilar artery thrombosis and occlusion of perforating or paramedian arteries).

The clinical features of some VB artery occlusions may make it very difficult to identify the time of symptom onset to assess the time limits for reestablishing blood flow. Fluctuating symptoms and progressive stroke leading to sudden deterioration, with coma and tetraparesis, is not uncommon. Furthermore, in our study, the frequency of patients in extremely poor clinical condition on admission may in part be attributed to the presence of VB artery occlusions for longer than expected from the statement of relatives or referring physicians. Unfortunately, this hypothesis cannot be tested using available data.

The clinical condition on admission proved to be a valuable prognostic factor. When coma and/or tetraparesis had been present for several hours, no difference in survival was apparent between Groups A and B (10 of 11 patients in each group), and no differential benefit of recanalization on survival was noted. Therefore, it would seem most important to begin treatment as soon as possible.

To determine prognostically significant angiographic or clinical findings, a number of combinations of admission status and occlusion patterns were tested. Of interest, 11 of 23 patients (47.8%) in extremely poor clinical condition on admission had MXD occlusion patterns, which are consistent with multiterritorial VB syndromes. The number of survivors with the combination of an extremely poor clinical condition on admission and a MID or MXD occlusion pattern (two of 16) was significantly lower than the number of survivors with the combination of a TOP or CVB occlusion pattern without an extremely poor clinical condition on admission (10 of 22). The question arises whether this significant result may be attributed to a more favorable natural history of TOP and CVB occlu-
sion patterns. This does not seem to be the case as only two of 11 patients in Group A and Subgroup B, who presented with the same clinical severity survived without recanalization compared with eight of 11 patients surviving in Subgroup B. All other patients died after several days, showing continuous deterioration of their symptoms leading to coma or the locked-in syndrome. This observation is of special interest as the group of TOP occlusions has been associated with a poor spontaneous outcome.

The issue of intracerebral hemorrhage following thrombolytic therapy has been addressed. In our study the incidence of hemorrhagic transformation among patients receiving thrombolytic therapy was four of 43 (9.3%), within the range reported for hemorrhage associated with infarction in the carotid artery territory. Interestingly, two patients exhibited hemorrhagic infarction in the absence of recanalization. No laboratory test results were indicative of the impending hemorrhage.

Despite the limitations of retrospective analyses of open studies and the limited information about the natural history of acute severe brainstem strokes due to VB artery occlusions, our study presents preliminary evidence that early recanalization of VB artery occlusion may be accompanied by a significant improvement in clinical outcome. Local intra-arterial infusion of thrombolytic agents in patients suffering from acute VB artery occlusion provides the following useful new insights: 1) recanalization of acute occluded cerebral vessels is possible, 2) recanalization can be achieved without an increased risk of intracerebral hemorrhage, and 3) recanalization is accompanied by a significant improvement of clinical outcome and survival.

With the advent and availability of thrombus-selective agents such as tPA, the safety and efficacy of intravenous infusion of such agents can be tested in acute thrombotic VB artery stroke in a carefully designed prospective fashion without the need to apply the agents by means of interventional neuroradiologic maneuvers. Although patient heterogeneity together with the relatively low frequency of VB artery occlusions make it difficult to recruit a large number of comparable patients in a double-blind study at a single center, the patient characteristics derived from our series will be helpful for the planning of future studies.

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References


KEY WORDS • anticoagulants • streptokinase • urokinase • vertebrobasilar insufficiency
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