Local Intra-arterial Fibrinolytic Therapy in Acute Carotid Territory Stroke
A Pilot Study
Gregory J. del Zoppo, MD, Andreas Ferbert, MD, Shirley Otis, MD, Hartmut Brückmann, MD, Werner Hacke, MD, Jack Zyroff, MD, Laurence A. Harker, MD, and Hermann Zeumer, MD

The possibility that intra-arterial local infusion of fibrinolytic agents may achieve recanalization of previously occluded carotid territory arteries in acute stroke was tested in a prospective angiography-based open pilot study at two centers. Fifteen of 20 patients with acute symptoms (mean treatment-onset interval 7.6 hours) demonstrated complete recanalization; 10 of the 15 patients exhibited clinical improvement of varying degree by the time of hospital discharge. Four of the 20 patients suffered hemorrhagic transformation of the infarcted territory without clinical deterioration or demise. Because of the study format and the limited number of patients, dose responses for recanalization and risk relations were not established. We conclude that local intra-arterial fibrinolytic therapy may lead to cerebral arterial recanalization in acute carotid territory thrombotic stroke. The particular implications and limitations of this approach are discussed. (Stroke 1988;19:307–313)

The theoretical basis for the use of thrombolytic agents in patients with symptoms of cerebral ischemia derives from the observation that the majority of acute strokes result from atherothrombotic or thromboembolic processes. Early studies using intravenous infusions of fibrinolytic agents in stroke patients sought to demonstrate favorable clinical outcome, the presence or absence of central nervous system hemorrhage, and, in some instances, evidence of arterial recanalization. The subsequent interpretation that fibrinolytic agents administered systemically may be of little benefit and may produce intracerebral hemorrhage has led to a general contraindication for their use in stroke. However, recent criticisms of study design and methods have suggested that the safety and efficacy of the use of fibrinolytic agents in acute stroke have not been adequately tested.

To test the hypothesis that intra-arterial local infusions of fibrinolytic agents (urokinase, streptokinase) may achieve recanalization of the previously occluded appropriate brain-supplying artery in acute stroke, a prospective angiography-based pilot study of acute carotid territory stroke patients was undertaken at two centers. The principal positive outcome event was angiographically demonstrated recanalization of the occluded artery with clinical improvement, whereas the principal negative outcome event was the appearance of a high-attenuation lesion on unenhanced computed tomography study (CT scan) consistent with intracerebral hemorrhage, with associated clinical deterioration. Results of our experience with 20 patients are reported here in detail, with special attention to the circumstances and potential difficulties that might be encountered by this approach.

Subjects and Methods
Patients presenting with stable acute symptoms of carotid territory cerebral ischemia between January 1983 and May 1986 were studied at the Rheinisch-Westfälische Technische Hochschule (RWTH), Aachen, Federal Republic of Germany, and the Scripps Clinic and Research Foundation (SCRF), La Jolla, California. The study design and informed consent requirements were approved by the Human Subjects Committee (Institutional Review Board) or Ethics Committee of both institutions. All patients and/or their representative(s) provided informed consent before entry into the pilot study.

Definitions
For the purposes of this study acute stroke was defined as stable neurologic events (e.g., significant unilateral motor deficits with or without aphasia) suggestive of cerebrovascular occlusion occurring within 6–8 hours before the initiation of treatment. Occlusions within the carotid territory, including the intracranial internal carotid artery (ICA) and/or its major branches (the anterior cerebral artery [ACA],
middle cerebral artery [MCA], and posterior cerebral artery [PCA]) were studied.

Patient Characteristics

Twenty consecutive patients (8 women, 12 men) were included in this study (Tables 1 and 2). Patients 1–17 have been included in a recent review. Ancillary conditions associated with carotid territory occlusions in this patient group included hypertension (n = 1), oral contraceptives (n = 3), and a history of transient ischemic attacks (TIAs) (n = 2).

Study Protocol

All patients were entered prospectively. Clinical and neuroradiologic inclusion criteria included age between 21 and 80 years, stable neurologic deficit(s) with onset ≤8 hours before the expected time of treatment, and informed consent. Baseline studies, an unenhanced cerebral CT scan demonstrating no low-attenuation lesions and no high-attenuation lesion consistent with intracranial hemorrhage and an initial angiogram demonstrating complete occlusion of a major brain-supplying artery in the carotid artery distribution appropriate to the acute symptoms, were also required.

Clinical exclusion criteria included a history of intracranial pathology including intracranial hemorrhage; a history of fixed neurologic deficit(s) of ≤6 weeks duration; a history or evidence of malignant hypertension; a known hemorrhagic diathesis, uncompensated factor deficiencies, or concomitant anticoagulant therapy; conditions, except acute thrombotic disease, coma). Neuroradiologic exclusion criteria included the presence of incomplete arterial occlusion(s), intracranial tumor(s), arteriovenous malformation, aneurysm, or arterial dissection.

After acceptance into the study, patients were prepared in the neuroradiologic facility to receive the fibrinolytic agent by intra-arterial infusion via the angiographic system routinely employed for the initial diagnostic study at the respective institution.

Repeat selective angiograms of the treated brain-supplying artery were performed immediately following completion of the directed intra-arterial infusion. The patients were then returned to the (neurologic) intensive care unit for observation and follow-up care. Serial daily neurologic examinations were performed until discharge; CT scans were performed in all patients at least once before discharge, usually within 24–48 hours of the infusion, and later. The study was concluded when the patients were transferred, were discharged, or died.

Intra-arterial (Local) Infusion

Either urokinase (Actosolv, Behringwerke AG, Marburg, F.R.G.; at RWTH) or streptokinase (Streptase, Hoechst, Somerville, New Jersey; at SCRF and at RWTH) was employed for catheter-directed intra-arterial infusion. The respective dose-rate ranges used at RWTH were 40–300 x 10³ IU urokinase for 1.0–4.0 hours or 6–7 x 10³ IU streptokinase for 0.5–2.0 hours; at SCRF 250 x 10³ IU streptokinase was infused for 1.0 hour. At attempt was made at RWTH to undertake a dose-rate response study with urokinase by increasing dose and then infusion duration (Table 1); however, because of practical limits to the infusion duration and the variety of occlusion locations a formal dose-rate response study was not completed.

Initial attempts at local infusion were conducted through the original catheter system, which allowed only regional perfusion. Subsequently, superselective catheter systems, that is, a controlled-leak balloon catheter (Ingenor, Paris, France) positioned via a hydraulic propulsion system (Becton Dickinson, Rutherford, New Jersey) through the guiding catheter, were chosen for intra-arterial (local) infusion at both institutions. These systems allowed local infusion for up to 3 hours.

Ancillary Medical Management

Following local infusion of the fibrinolytic agent, patients received medical management considered routine for stroke patients in their respective geographic regions. At RWTH patients received concomitant intravenous heparin (500 IU/hr) with hydroxyethyl starch during their intensive care management, initiated within 1–3 hours after completion of infusion of the fibrinolytic agent. Anticoagulants and hemodilution therapy were not used at SCRF.

Outcome Events

The positive outcome event, angiographically demonstrated recanalization of the previously occluded carotid territory brain-supplying artery with clinical improvement, was judged by the primary neuroradiologist to be either no perfusion of the specified completely occluded cerebral artery, partial perfusion, or complete return of perfusion following infusion of the thrombolytic agent. Partial perfusion consisted of residual occlusion of the principal artery or perfusion of only some of the previously occluded major branches.

The negative outcome event, the appearance of a high-attenuation lesion on the postinfusion unenhanced CT scan consistent with an intracerebral hemorrhage with associated clinical deterioration, was regarded as either hemorrhagic infarction (without clinical deterioration) or cerebral hematoma, that is, parenchymatous hemorrhage with mass effect and clinical deterioration.

Clinical outcome was judged as improvement or no improvement in the motor deficit in relation to intracerebral hemorrhage and status at transfer or hospital discharge compared with the neurologic deficits on admission. All neurologists were advised to assess the clinical status of the patient upon evidence of cerebral hemorrhage and at hospital discharge compared with that at admission in addition to their daily assessment of patient progress. Complete/near-complete or partial motor improve-
ment constituted clinical improvement, whereas no change or deterioration/death constituted no clinical improvement. No quantitative neurologic scale was employed in our pilot study.

Data Review

All judgments were made in a prospective fashion during the course of patient care. A retrospective examination of all patient records provided the basis for final clinical assessment. An unblinded review of all radiographic studies demonstrated concurrence with the prospective judgment with regard to the presence or absence of arterial occlusion on initial angiography, the degree of postinfusion perfusion of the specified artery, and the presence or absence of intracerebral hemorrhage.

Statistics

Recanalization and clinical outcome data were tested by $\chi^2$ analysis.

Results

Patient Characteristics

Twenty consecutive patients (16 at RWTH, 4 at SCRF) with symptoms of acute carotid territory stroke who fulfilled all inclusion and no exclusion criteria were studied (Table 1). Because of the specific neuroradiographic outcome events studied, an untreated control group was not employed.

The distribution of probable etiologies of the arterial occlusions is given in Table 2. When the local cause was not obvious, an attempt was made to define a

<table>
<thead>
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<th>Table 1. Characteristics of Patients With Acute Carotid Territory Stroke Enrolled in Pilot Study of Intra-arterial Fibrinolytic Therapy</th>
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<tbody>
<tr>
<td>Patient/age/sex</td>
</tr>
<tr>
<td>ICA siphon</td>
</tr>
<tr>
<td>3/32/F</td>
</tr>
<tr>
<td>17/46/F</td>
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<tr>
<td>Carotid “T” (Cl segment)</td>
</tr>
<tr>
<td>4/51/F</td>
</tr>
<tr>
<td>8/62/F</td>
</tr>
<tr>
<td>16/46/F</td>
</tr>
<tr>
<td>Ipsilateral ICA + MCA embolus</td>
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<tr>
<td>10/53/M</td>
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<tr>
<td>11/64/M</td>
</tr>
<tr>
<td>15/68/M</td>
</tr>
<tr>
<td>MCA and/or MCA branch</td>
</tr>
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<td>1/60/F</td>
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<tr>
<td>2/48/M</td>
</tr>
<tr>
<td>5/53/F</td>
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<td>6/28/F</td>
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<td>20/57/M</td>
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<td>PCA</td>
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$\Delta$T–O, interval between symptom onset and treatment; U, urokinase; S, streptokinase; Duration, duration of local intra-arterial infusion; Recanalization, (angiographically confirmed) residual occlusions are noted, see text; +, hemorrhagic infarction/parenchymatous hemorrhage; –, no abnormality determined by unenhanced cerebral computed tomography scan; C/N, complete/near-complete symptom resolution; P, partial symptom resolution; U, unchanged; D, deterioration/death; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; F, female; M, male.
TABLE 2. Source/Etiology of Carotid Territory Occlusions

<table>
<thead>
<tr>
<th>Location</th>
<th>Count</th>
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<tbody>
<tr>
<td>Cardiogenic</td>
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<tr>
<td>Cardiomyopathy</td>
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</tr>
<tr>
<td>Valvular</td>
<td>3</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>2</td>
</tr>
<tr>
<td>ICA stenosis</td>
<td>2 (3)</td>
</tr>
<tr>
<td>MCA stenosis</td>
<td>(1)</td>
</tr>
<tr>
<td>Angiography</td>
<td>1</td>
</tr>
<tr>
<td>Interventional procedure</td>
<td>3</td>
</tr>
<tr>
<td>Hemostatic abnormality</td>
<td>0</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; MCA, middle cerebral artery. Numbers in parentheses are those apparent angiographically following fibrinolysis.

cardiac source by electrocardiography, two-dimensional echocardiography, and 24-hour continuous cardiac monitor. Only two patients had a history of premonitory TIA, one associated with proximal ICA stenosis, the other with a proximal MCA stenosis.

Location of Arterial Occlusions

The distribution of angiographically defined arterial occlusions (Table 1) confirmed the impression that the majority of clinical deficits resulted from MCA occlusions. The identified arterial occlusions included isolated lesions at the ICA siphon (n = 2) and the ICA “T” (n = 3), in the ipsilateral ICA with an MCA embolus (n = 3), in an isolated M1 segment of the MCA proximal to the take-off of the lenticulostriate arteries (LSAs) (n = 6), in the MCA distal to the LSA (M2 segment) and/or MCA branch(es) (n = 5), and a PCA occlusion (n = 1). The latter finding accompanied an acute right flaccid hemiparesis and left conjugate ocular deviation in a patient with a mitral valve prosthesis.

Outcome

Following local intra-arterial infusion of urokinase or streptokinase, complete recanalization was documented by angiography in 15 patients within 24 hours of the baseline study (Table 3). Ten of the 15 patients demonstrated partial to near-complete resolution of the neurologic (motor) deficits, whereas the two patients who did not demonstrate recanalization underwent no clinical improvement. Partial recanalization (residual stenosis or recanalization of some branches) occurred in three patients (Table 1).

Interval From Symptom Onset to Treatment

By protocol, all patients were to receive the fibrinolytic agent within 8 hours after apparent symptom onset; however, a review of the admission histories indicated that three patients (19, 5, and 1, respectively) had the onset of symptoms or premonitory events 10, 20, and 24 hours before treatment. Importantly, nine of 10 patients demonstrating clinical improvement received the intra-arterial infusion within 4–8 hours after symptom onset (Figure 1). The timing of the three deaths was not related to a treatment-onset interval. An inverse relation between clinical outcome and treatment-onset interval, that is, maximal clinical improvement at earliest intervention, is not evident from these data.

Three patients (12, 17, and 18) had carotid territory embolic events as complications of interventional angiographic procedures, which led to local infusion of a fibrinolytic agent. Of interest, despite initiation of thrombolysis within 1 hour after symptom onset with subsequent complete recanalization in all cases, no clinical improvement was demonstrated.

Intracerebral Hemorrhage

Four patients (4, 11, 13, and 19) suffered CT-detectable intracerebral hemorrhages within 24 hours after intra-arterial infusion (Figure 1); however, no clinical deterioration or death could be attributed to the intracerebral hemorrhage. All four hemorrhagic events occurred in the 15 patients who demonstrated complete arterial recanalization (Table 3). The hemorrhagic transformations were consistent with hemorrhagic infarctions by CT appearance and absence of clinical worsening; each hemorrhage resolved during hospitalization. Three of the four patients demonstrated clinical improvement in the face of the hemorrhage. All patients who hemorrhaged had been given concomitant...
heparin with hydroxyethyl starch in the immediate postinfusion period. All hemorrhagic infarctions occurred in the affected LSA territory; no CT-detectable hemorrhagic event occurred in the two patients with large hemispheric infarctions (7 and 15).

Complications of Angiography
No patient in this study deteriorated acutely during angiography, before or after the infusion.

Regional vs. Local Perfusion
Of seven patients (7, 10, 11, 12, 14, 18, and 19) with proximal (M1 segment) MCA occlusions, complete MCA recanalization was achieved in five treated locally via a superselective catheter. The two remaining patients (7 and 15), in whom no opening of the M1 occlusion occurred, received regional perfusion of the thrombolytic agent with the catheter positioned at the proximal ICA.

Deaths
Three patients died during the study. All had proximal (M1 segment) MCA occlusions, and two (7 and 15) developed hemispheric lesions associated with mass effect in association with a nonrecanlized proximal MCA occlusion.

Discussion
Our prospective pilot study sought to test the ability of local intra-arterial infusion of conventional fibrinolytic agents (urokinase and streptokinase) to mediate recanalization when carefully delivered proximal to an angiographically-defined cerebral artery occlusion in consecutive patients with acute carotid territory stroke. The efficacy of local intra-arterial infusion of urokinase and/or streptokinase for coronary artery thrombosis in acute myocardial infarction41718 served as a critical model for our study. Theoretical considerations of the mode of action of streptokinase/urokinase19-20 and reports of limited experience in vertebrobasilar arterial thrombosis and in select carotid territory thrombosis have suggested potential success with this approach in acute stroke.12-23 However, the variables underlying success and failure remain undefined in acute carotid territory stroke. Inherent in our study is the frequency of atherothrombotic embolic arterial occlusions responsible for acute stroke.1 Because of strict clinical and neuroradiographic inclusion/exclusion criteria and the logistics of patient enrollment at each center, we could not determine the frequency of appropriate cerebrovascular occlusions associated with the acute strokes (or the total number of patients with symptoms) satisfying those criteria. At both centers, the number of candidate patients who satisfied all clinical inclusion and no exclusion criteria, without appropriate arterial occlusion on angiography, was small, < 30%.

A complete recanalization rate of 75% was achieved in our study, a rate similar to that observed for local thrombolytic therapy in acute myocardial infarction patients.1718 The relevance of this thrombolytic recanalization rate to the spontaneous recanalization rate in acute carotid territory stroke cannot be determined from data currently available.24 While our study was intended to evaluate thrombolysis in the carotid arterial system and the frequency of intracerebral hemorrhage, we also assessed clinical outcome. Because no prospectively verified scoring instrument with predictive value for clinical outcome has been described,25 we elected to employ a simple two-tiered assessment of clinical (neurologic) outcome. Regarding the two clinical categories, improvement and no improvement, no significant difference between the recanalization with improvement and the no recanalization with no improvement categories was obtained. Five more patients with occlusions that did not recanalize and who did not improve neurologically would have been necessary to achieve a difference that was significant (p = 0.05). At this time, clinical assessment alone is inadequate to judge the efficacy of this intervention relative to the natural history of acute carotid territory thrombosis.

It has been suggested that in focal ischemia, reestablishment of blood flow in the occluded cerebral artery and its dependent tissue should be achieved within 6 hours after symptom onset.26-29 Attempts to treat acute stroke patients within that time exposed several important considerations relative to the study of carotid territory strokes. First, fulfillment of the entrance requirements, including the time necessary to complete the baseline CT and angiographic studies, allowed the majority of the patients to be entered within 8 hours. Three patients treated within 1 hour after symptom onset would have been expected to achieve significant clinical improvement; however, deficits remained in two patients and the third patient died, suggesting that in acute M1 segment MCA occlusions, cerebral injury in some patients may be sufficiently critical and extensive as to allow little functional recovery despite early recanalization. Second, accurate assessment of the time of symptom onset may be difficult during the initial hours of clinical evaluation, as demonstrated by three patients who were found retrospectively to have been treated > 10 hours after first symptoms. Also, exclusion of TIAAs as the "initial" symptom may be difficult. In our series, patients treated > 10 hours after symptom onset demonstrated little neurologic improvement. Third, although presenting symptoms suggested extensive carotid or MCA territorial ischemia, in some patients only distal branch occlusions were documented at angiography, suggesting downstream thromboembolism from more proximal occlusions. Therefore, angiographic demonstration of distal branch occlusions may not reflect the potential and clinically relevant initial extent of cerebral ischemia. Finally, the clinical outcome following thrombolytic therapy is probably most significantly influenced by the collateral arterial supply of the ischemic tissue.25

The position of the infusion catheter relative to the arterial occlusion may be relevant to lysis of carotid territory thrombi. Two patients with M1 segment...
occlusions in whom the fibrinolytic agent was infused at the carotid bifurcation did not achieve MCA recanalization despite a documented systemic fibrinolytic effect (data not shown), whereas five patients who received the agent near the origin of the MCA achieved recanalization. In the former cases, the specific flow characteristics of the circle of Willis may divert thrombolytic agents directed toward thrombi in the proximal MCA, thereby reducing the concentration of regionally infused fibrin-nonselective agents. It remains to be seen whether intravenous infusion of the fibrin-selective thrombolytic agents tissue plasminogen activator (tPA) or single-chain plasminogen activator (scuPA) are more effective for M1 segment MCA occlusions although recent experience with fibrinolytic agents in acute coronary artery thrombosis has remobilized the discussion regarding hemorrhagic risk associated with intracranial hemorrhage..

In our study four of 20 patients (20%) developed hemorrhagic transformation without associated mass effect or clinical deterioration. All hemorrhagic infarctions were located in the corpus striatum of the affected hemisphere and were associated with recanalization of the subtending artery. The relative contributions of thrombolysis, re-establishment of blood flow, thrombus lysis per se, the anticoagulant effects of fibrin(ogen) degradation products, and the inactivation of plasma factors V and VIII for the hemorrhagic events could not be determined. However, all patients who bled received a hemodilutional agent with or without heparin in the early postischemic period. Such volume-expanding agents have known antiplatelet and anticoagulation properties.

The spontaneous hemorrhagic conversion rate following conventional therapy in stroke is between 0 and 43%, based upon retrospective analyses and a handful of prospective studies. The incidence of hemorrhage (20%) in our pilot study falls within the rather broad range reported. In the one prospective CT-based study of a design comparable to that of our study, the 28 patients (43%) who hemorrhaged each received a hemodiluitional agent and heparin and/or salicylates, a significant association. While the expected incidence of hemorrhagic conversion in patients treated with fibrinolytic agents for acute carotid territory stroke is unknown, it would be expected that concomitant use of anticoagulant and hemodiluational agents would augment the unknown hemorrhagic risk. Of interest to future studies, an additive effect of heparin with tPA augments the unknown hemorrhagic risk. Of interest to future studies, an additive effect of heparin with tPA would be expected that concomitant use of anticoagulant and hemodiluational agents may contribute to the risk of intracerebral hemorrhage and possible clinical deterioration. To address the questions of safety and efficacy, a carefully designed prospective study in two stages will be necessary: an initial determination of the agent dose-rate capable of achieving recanalization without hemorrhage, and a second prospective study with a larger patient base comparing clinical outcome and hemorrhagic potential between fibrin-selective thrombolytic agents and competing therapy.

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References


KEY WORDS • acute stroke • carotid territory • fibrinolysis • urokinase/streptokinase
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