Early Intravenous Thrombolysis for Acute Ischemic Stroke in a Community-Based Approach

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Background and Purpose—Controlled multicenter studies have demonstrated the efficacy of systemic recombinant tissue-type plasminogen activator (rtPA) treatment in selected cases of acute ischemic stroke. The feasibility of this therapeutic option in clinical practice was assessed in a community-based approach.

Methods—We offered rtPA treatment to stroke patients in a prospective open-label monocenter study applying inclusion criteria similar to those of the National Institute of Neurological Disorders, and Stroke study. In order to treat patients within 3 hours of symptom onset, a referral system was used by which eligible patients from all over the city of Cologne, Federal Republic of Germany, were rushed to the Department of Neurology of the University Hospital. We present data on the effectiveness of the referral system and the outcome results of the first 100 consecutive patients treated within an 18-month period.

Results—Of 453 consecutive patients with a presumed diagnosis of acute stroke referred to our department between March 1996 and August 1997, 100 patients (22%) were treated with intravenous thrombolysis, 26% of them within 90 minutes of symptom onset. The average time from stroke onset to arrival at our department was 78 minutes, and from arrival to treatment 48 minutes. After 3 months, 53 patients recovered to fully independent function. The rates of total, symptomatic, and fatal intracerebral hemorrhage were 11%, 5%, and 1%, respectively. Overall mortality was 12%.

Conclusions—Thrombolysis with rtPA was effectively applied in routine management of stroke patients in a community-based approach with acceptable efforts and without additional costs. Under these circumstances, outcome and complication rates were comparable to those of multicenter trials. (Stroke. 1998;29:1544-1549.)

Key Words: stroke management ■ stroke, acute ■ thrombolytic therapy

Controlled multicenter studies with rtPA demonstrated for the first time an effective treatment for selected cases of acute stroke.1-3 The next necessary step is to introduce the experiences from the positive trials into clinical routine and to carefully monitor the results.4 However, this therapeutic option bears a potential risk of intracerebral hemorrhage, and its major shortcoming for routine application is the short therapeutic window of <3 hours. In addition, it is recommended that the application of thrombolysis should be restricted to neurologists or other disciplines with expertise in neurological emergency and CT reading.5,6 In Cologne, only our department met the criteria described above at that time. With these limitations, we offered rtPA treatment in a community-based approach to stroke patients in a prospective open-label study applying inclusion criteria similar to those of the NINDS study. A referral system was used by which eligible patients from all over Cologne were rushed to our department. The feasibility of early thrombolysis for patients with acute ischemic stroke in this setting was assessed. In addition, outcome and complication rates were analyzed and compared with those of the NINDS and ECASS-I trials.

Subjects and Methods

Patients and Recruitment

With a city area of 156 square miles and 1 004 928 inhabitants, Cologne is the third largest city in Germany in terms of area and the fourth largest in terms of population. There are 14 community hospitals without a neurology department, 7 of them with a CT scanner but only 2 of them with 24-hour-service. One teaching hospital with a neurology department and CT scanner with 24-hour service had decided not to offer thrombolysis at that time. Thus, our neurology department at the University Hospital was the only place where patients could receive thrombolytic therapy. In case of stroke, patients are usually referred by the emergency services to the community hospitals nearest to their homes. A cooperation between the community hospitals and our department was established several years ago in order to optimize acute stroke management. With systemic thrombolysis introduced in our department in March 1996 as a promising therapeutic strategy, this referral system was activated, and its effectiveness was significantly improved by inclusion of the municipal emergency services. The cooperative strategy was to offer rtPA therapy to as many suitable patients as possible. Preselective criteria to refer patients to our department were restricted to the following: onset of symptoms suspicious of stroke within less than 3 hours, patient age under 80 years, and absence of severe impairment of consciousness. If referred patients were not eligible for thrombolytic treatment, they were sent to their commu-
treatment. Early clinical improvement was defined according to the baseline examination and had not been present during the initial 3 days. The outcome at 3 months was determined by 2 trained examiners (S. Schmülling and S. Schneweis) who had not performed the initial CT examination. Definitions of time intervals were established before data collection. Failure to define etiology was classified as undetermined cause.12 Patients were classified into the diagnostic subgroups of large-vessel atherosclerosis, small-vessel lacunar, and cardiogenic embolism. Failure to define etiology was classified as undetermined cause.15

Inclusion Criteria, Clinical Assessment, and Treatment
Inclusion and exclusion criteria for systemic rtPA treatment were adopted from the NINDS study, with the following additional exclusion criteria taken from the ECASS study:2 Age over 80 years, hypodensity of more than 33% of the middle cerebral artery territory on initial CT scan, severely impaired consciousness (except for kin, 0.9 mg/kg rtPA [alteplase {Actilyse}, Thomae] was administered intravenously over 60 minutes (10% bolus, 90% continuously). In contrast to former studies, immediate anticoagulation with heparin was routinely performed. This was done for early secondary prophylaxis and analogous to coronary thrombolysis. After completion of rtPA infusion, heparin was administered by continuous infusion, aiming to increase aPTT to 1 1/2 to 2 times standard normal values. Initial dosage of heparin infusion was 1000 U/h. aPTT was repeatedly controlled, and dosage was adjusted for the duration of heparin therapy (approximately 10 days). All patients received osmodiuretic drugs (mannitol 10%, in rare cases glycerol 10%, 500 mL per day, in 5 doses of 100 mL each) during the first day to prevent brain edema. Osmotherapy was continued only if brain edema was detected in the following CT examination.

Outcome Assessment
Clinical assessment was repeated with NIHSS after 24 hours and after 90 days. In addition, activities of daily living were measured using the Barthel Index (0 to 100 points),3 and overall function was assessed using the modified Rankin scale (grade 0 to 5)2 after 90 days. The outcome at 3 months was determined by 2 trained examiners (S. Schmülling and S. Schneweis) who had not performed the initial clinical examination and had not been present during the initial treatment. Early clinical improvement was defined according to the NINDS criteria as 4-point improvement in the NIHSS score from baseline values or complete resolution of neurological deficit. Classification of late outcome was also adopted from the NINDS study. Late outcome data were compared with those of the NINDS study. Rankin score at day 90 was also compared with the 3-hour cohort of the intention-to-treat population of the ECASS trial.10

Statistical Analysis
Data were analyzed using SAS procedures (SAS Institute Inc). The values were expressed as mean±SD, and comparisons of baseline characteristics among groups were performed with Wilcoxon’s signed rank test. Potential predictors of intracerebral hemorrhage were analyzed by Fisher’s exact test for dichotomous variables.

CT Scans
Unenhanced head CT scanning with a Siemens Somatom Plus 32 scanner was routinely performed on admission, at 24 hours, and after 1 week and whenever neurological deterioration occurred. Initial CT scans were scrutinized for early signs of infarction defined as a hypodensity and for indications of hemorrhage, and follow-up scans for demarcation of infarction, extent of brain edema, and hemorrhagic conversion. This was done independently by a neurologist (C.S.) who had participated in the ECASS CT training but who had no knowledge of the clinical data of the patients and follow-up CTs. Hemorrhage was classified as hemorrhagic infarction or parenchymal hemorrhage according to the criteria described by Pessin et al.11 The latter were then subdivided into symptomatic hemorrhages and asymptomatic hemorrhages.3

Etiologic Data
Classification of stroke was based on the information available at discharge after thorough examination that included Doppler ultrasonography of extra- and intracranial vessels and both echocardiography and Holter-ECG in cases of suspected cardiac embolism. Patients were classified into the diagnostic subgroups of large-vessel atherosclerosis, small-vessel lacunar, and cardiogenic embolism. Failure to define etiology was classified as undetermined cause.15

Results
Epidemiological Background
Between March 1997 and May 1997 (3 months), 672 patients with presumed acute stroke were admitted to the Cologne hospitals. In 325 patients (48.4%) the final diagnosis was acute ischemic stroke, in 136 (20.2%) patients transient ischemic attack, and in 35 (5.2%) patients hemorrhage; in 93 (13.8%) patients final diagnosis was not established because no CT scan was performed. In 69 (10.5%) patients final diagnosis was something other than stroke (eg, metabolic disease or infection); in 14 (2%) patients final diagnosis was missing. In 64 (20%) of 325 patients with the final diagnosis of acute ischemic stroke, no reliable information about symptom onset was available. Ninety-six (29.5%) patients with the final diagnosis of acute ischemic stroke were admitted to a Cologne hospital within 3 hours after symptom onset, 67 of them were under age 80 years. From these data the following estimates can be made for an 18-month period (Figure 1).

Treatment Group
Between March 1996 and August 1997, 453 consecutive patients were referred to our department with presumed acute stroke. Of those, 230 (50.8%) patients were referred by the emergency services, 196 (43.3%) patients from a community hospital, and 27 (5.9%) patients from a general practitioner.
Forty-eight (10.6%) patients were initially misdiagnosed, 29 of them with neurological disease (eg, epileptic seizures with Todd’s paresis, meningoencephalitis, or psychiatric disorders), 19 of them with nonneurological disease (eg, intoxication, syncope, or metabolic disorder). In 84 (18.5%) patients, CT scanning revealed intracerebral brain hemorrhage. Seventy-six (16.8%) patients showed rapid improvement or full resolution of clinical symptoms. In 245 (54%) patients, the diagnosis of acute ischemic stroke was established. In 96 of these patients, however, the time of onset was longer than 3 hours before admission or could not be defined reliably. Therefore, only 149 (32.9%) patients matched our preselective criteria. Of these 149 patients, 47 patients had to be excluded because of the presence of predefined exclusion criteria (eg, excessive hypertension, pretreatment with anticoagulants, early major infarct signs on CT, or recent major surgery), 2 patients refused consent. Finally, 100 patients (22% of the patients referred) were treated with systemic rtPA (Figure 1). In 2 of them, the protocol was violated (cases 1 and 9), because they were treated even though contradicting the information available on admission, severe symptoms had been present on awakening from sleep so that symptom onset could not clearly be defined and probably was longer than 3 hours previous. They both died from transtentorial herniation due to severe space-occupying edema within the first week after treatment. Sixty-one treated patients were transported directly from their homes to our hospital by the emergency medical services with a mean arrival interval of 68 minutes. Thirty-one patients were transferred from another hospital and mean arrival interval was 81 minutes. The difference in arrival interval between these groups was statistically significant (P<0.0001). Mean time from arrival at our department to initiation of treatment (“door-to-needle time”) was 48 minutes (SD, 25 minutes; range, 20 to 130 minutes). Thirty-four patients were treated 30 minutes or less after arrival.

**Effect of Thrombolysis**

The baseline characteristics of the 100 patients treated with thrombolysis are given in the Table in comparison to the NINDS I and II subpopulations. The frequency of cardiovascular risk factors was comparable between the NINDS study and our cohort. Eighty-eight patients suffered from supratentorial stroke, and 12 patients from infratentorial stroke. Early improvement (within the first 24 hours) was found in 53 patients, 17 of them had normalized after 24 hours. Late outcome for the whole population (all data in percent of the respective population) in comparison with NINDS and ECASS 3-hour intent-to-treat population cohort results is shown in Figure 2.

### Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NINDS rt-PA, Part I (n=144)</th>
<th>NINDS rt-PA, Part II (n=168)</th>
<th>Cologne (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>67±10</td>
<td>69±12</td>
<td>63±11</td>
</tr>
<tr>
<td>Time to treatment, minimum and mean</td>
<td>48% within 90 min</td>
<td>124 min</td>
<td>26% within 90 min</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>42</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±15</td>
<td>76±16</td>
<td>75±15</td>
</tr>
<tr>
<td>NIHSS score, median (range)</td>
<td>14 (1–37)</td>
<td>14 (2–37)</td>
<td>12 (2–37)</td>
</tr>
<tr>
<td>Small-vessel, %</td>
<td>19</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Large-vessel, %</td>
<td>35</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>Cardioembolic, %</td>
<td>42</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Other/Undetermined, %</td>
<td>3</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>155±22</td>
<td>153±22</td>
<td>161±23</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85±12</td>
<td>85±14</td>
<td>93±13</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>332±94</td>
<td>311±102</td>
<td>303±98</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>149±76</td>
<td>149±66</td>
<td>141±68</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
Twelve patients died during the 90-day observation period, 8 of them during the first week. One patient died from parenchymal hemorrhage, 7 from malignant brain edema, and 1 with infratentorial stroke from brain stem dysfunction and additional supratentorial hemorrhage. One patient died during carotid artery surgery on day 43, 1 patient died from septic pneumonia on day 74, and 1 from sudden cardiac arrest on day 44. The latter 3 deaths were considered to be unrelated to the treatment of acute stroke.

Early infarct signs on CT defined as hypodensity covering less than one third of the MCA territory were present in 31 patients (35% of the supratentorial ischemias).

Hemorrhagic Complications

Hemorrhagic infarction occurred in 7 patients, in 1 of them hemorrhagic infarction was associated with neurological deterioration. Asymptomatic parenchymal hemorrhage occurred in 6 patients and symptomatic parenchymal hemorrhage in 5 patients. Incidence of hemorrhagic conversion was neither significantly related to baseline NIHSS nor to aPTT values after 24 hours. After 24 hours, 31 patients were undercoagulated, in 36 patients aPTT values were within the target range and 33 patients were over-anticoagulated. Compared with the group of patients without hemorrhagic conversion, incidence of ASA pretreatment (9/30 versus 9/70, \(P=0.01\)), history of myocardial infarction (6/15 versus 12/85, \(P=0.002\)), and incidence of early infarct signs on CT (9/31 versus 8/57, \(P=0.02\)) were significantly higher in the hemorrhagic conversion group. In the 1 patient pretreated with ticlopidine, devastating symptomatic parenchymal hematoma occurred during rtPA infusion and before initiation of heparin treatment.

Discussion

This report presents data from an open therapeutic trial in which early systemic thrombolysis with rtPA was offered in the setting of a community-based monocenter approach. The trial followed a strict protocol and was prospective, but was not blinded, and did not include a parallel control group. Therefore, this study cannot provide evidence for the efficacy of treatment, but it supports the feasibility of intravenous thrombolysis for patients with acute ischemic stroke in clinical practice. The main point addressed in this study is the power of a cooperative system to refer patients potentially suitable for thrombolysis to a single center within the short therapeutic window. In addition, outcome and safety results of systemic thrombolysis in this setting are compared with those of multicenter trials.

Patient Referral System

Thrombolysis is an effective but potentially harmful treatment, and there is only limited experience from 2 large placebo-controlled trials and a few open trials.\(^{1,2,13-20}\) Therefore, it is presently recommended that thrombolysis should be restricted to neurologists and other specialties with expertise in neurological emergency and CT reading. Since these criteria cannot be met in any of our community hospitals, there are 2 possible cooperative strategies for putting thrombolysis into clinical practice: One is to establish communication systems between the hospitals and stroke teams examining the patients on-site before the decision to initiate thrombolysis. This would mean additional manpower and consequently additional costs. On the other hand, the reliable selection of suitable patients would be performed in a clinical setting, and there would be no unnecessary further time-consuming transportation of the patient. Furthermore, competition between hospitals would be avoided. The second strategy is a monocenter approach using a referral system. The advantage of this strategy is that the whole staff of one center can be trained and in-hospital management can be optimized. Because the capacity regarding the number of patients that can adequately be managed in a single center is...
limited, an effective referral system is needed to preselect patients without losing too much time. To achieve that goal, the emergency services and the community hospitals were provided with preselective criteria that are easy to handle on the one hand and effective on the other hand.

Within an 18-month period 149 patients who met these criteria perfectly were referred to us; of these, 100 were treated with thrombolysis. This fact underlines the effectiveness of the system on the one hand and the effectiveness of our center on the other hand. Whereas arrival times are somewhat longer, especially for those patients referred from a community hospital, than in the recently published first American feasibility study, this difference was compensated for by our extremely short door-to-needle time (average of 48 minutes compared with 100 minutes in the American study).

This gives evidence of a successful optimization of in-hospital management that would be hard to achieve in all centers in the alternative multicenter approach. Despite additional exclusion criteria, we were able to treat the largest series of patients in a single center ever reported. Our aim for the future is to optimize preselection (eg, by stressing the importance of the exact time of symptom onset) and to increase the number of patients eligible for thrombolysis. Because late arrival still is a major limiting factor for early thrombolysis, a public educational program was started by which potential patients, their relatives, and the general medical community are informed about signs and symptoms of ischemic events and the chances and potential benefits of emergency management of stroke. In 2 studies in which public awareness and education were stimulated by intensive campaigns, intervals between onset of symptoms and arrival in specialized institutions were significantly shortened by increased use of emergency services.

Safety
Clinical and radiological assessment and therapeutic decision were made by the neurologists in charge of the intensive care unit. They had been made familiar with the protocol and the CT exclusion criteria and were trained in the use of the NIHSS. When we started the study in March 1996 we based our protocol on the experiences of the NINDS and ECASS studies. At that time, subgroup analysis of the ECASS study was already available indicating that patients with very severe strokes and major early infarct signs would not benefit from thrombolysis. In addition, except for the NINDS study, all studies had an upper age limit of 80 years. Therefore, these additional exclusion criteria were used. These modifications had an effect on our study population. As compared with the NINDS study population (median NIHSS of 14 and mean age of 67 and 69 years, respectively), our patients were less severely affected (median NIHSS of 12, mean NIHSS of 13) and younger (mean age of 63 years), but were comparable to the ECASS 3-hour intention-to-treat population (mean NIHSS of 13). Whether our additional exclusion criteria are still justified if the recently published subgroup analysis of the NINDS trial is taken into account should be a matter of discussion. Whereas age and deficit severity did not alter the likelihood of responding favorably to rtPA, the relevance of early infarct signs was not adequately analyzed because no differentiation between minor and major early infarct signs was made. The post hoc analysis of the ECASS data yielded convincing evidence that for patients treated within a 6-hour time window the response to rtPA can be predicted on the basis of initial CT findings of the extent of parenchymal hypodensity. Whether this also is true for patients treated within 3 hours after symptom onset needs further elucidation. The finding is important that in 35% of the patients treated who had supratentorial stroke, minor early infarct signs were detected on initial CT. These are the patients with an extended volume of critically hypoperfused tissue who are at risk to develop extended infarctions that can potentially be prevented by early reperfusion. Patients with major early infarct signs on CT were reliably excluded in our study: Not a single protocol violation could be detected at reevaluation of admission CT scans.

Other protocol violations were also rare: Only at the beginning of our study, 2 patients were treated even though they were ineligible for thrombolysis because of an elapsed time window. They both died from malignant brain edema following unsuccessful thrombolysis. This observation is in accordance with the finding that patients with protocol violations have higher complication rates and stresses the importance of careful patient selection, especially the exact definition of the time of onset of symptoms. Mistaking the moment of symptom recognition for the moment of symptom onset was a major pitfall for the first contacting doctors.

Incidence of symptomatic hemorrhage was not excessively high after combined treatment with rtPA and high-dose heparin, and independent of aPTT values after 24 hours. The finding that prior myocardial infarction was associated with a higher risk of intracerebral hemorrhage goes in line with the results of the univariate analysis of the NINDS data. Surprisingly, a relationship between baseline stroke severity and intracerebral hemorrhage could not be established in our patients, whereas a significant relationship between ASA pretreatment and intracerebral hemorrhage was detected. This might indicate that the combination of ASA, rtPA, and high-dose heparin should be avoided. Whether the devastating parenchymal hemorrhage seen during rtPA infusion in 1 patient can be attributed to his ticlopidine pretreatment cannot be answered, because he was the only patient pretreated with ticlopidine.

Outcome Results
Early and late results in our patients are slightly better than those of the NINDS trial and comparable to those of the ECASS 3-hour cohort. This might be due to the differences in stroke severity and age on admission. Age-by-deficit severity interaction has been shown to relate significantly to 3-month outcome.

Besides differences in the study populations, other factors could have also had a positive influence on our results: the use of intravenous heparin and the concomitant use of osmodiuretics. The same factors were suggested by Trouillas et al to be responsible for the excellent results in their open rtPA study. A definite assessment of the effectiveness of immediate heparin cannot be given because of the lack of a control group in our study. Even though heparin treatment
was recently shown not to be effective in stroke with therapy onset within the first 48 hours, it could play a role as adjunctive therapy in thrombolysis of stroke, as it does in myocardial infarction. Our data could therefore encourage a controlled trial to assess the potential benefit of combined therapy of rtPA and heparin.

In conclusion, in a community-based approach early intravenous thrombolysis was offered to a considerable number of stroke patients without additional cost (except for drug costs) and without expiring the limited capacity of a single stroke center. However, the number of potential candidates for thrombolysis is substantially higher. Therefore, further optimization of the referral system is necessary.

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