Intravenous tPA for Ischemic Stroke
Team Performance Over Time, Safety, and Efficacy in a Single-Center, 2-Year Experience

Hans-Christian Koennecke, MD; Roland Nohr, MD; Stefanie Leistner, MD; Peter Marx, MD

Background and Purpose—Safety and efficacy concerns toward thrombolysis for ischemic stroke prevail among many neurologists because of the risks of hemorrhage and the small proportion of suitable patients. We therefore prospectively assessed feasibility, safety, efficacy, and team performance in a single center to prove whether thrombolytic treatment is practical in daily clinical routine.

Methods—Patients were prospectively recruited over a 2-year period. Major inclusion and exclusion criteria from large, randomized controlled trials were combined. Prespecified outcome parameters were the modified Rankin scale (MRS) and the Barthel Index (BI) at 3 months and symptomatic hemorrhagic complications. In addition, certain time intervals during the diagnostic process preceding thrombolysis were prospectively recorded.

Results—Within 2 years a total of 75 patients underwent intravenous thrombolysis, corresponding to 9.4% of all admitted patients with stroke and 14.9% of patients with ischemic stroke. Mean±SD age was 68±13 (range 34 to 90) years; median baseline National Institutes of Health Stroke Scale score was 13±6 (range 2 to 34). Thrombolysis was started at an average time of 144 minutes after symptom onset, and 13 patients (17.3%) were treated beyond 3 hours. Two cerebral hemorrhages (2.7%) occurred. Outcome according to the MRS was good (MRS 0 to 1) in 40%, moderate (MRS 2 to 3) in 32%, and poor (MRS 4 to 5) in 13%; the corresponding results, as measured by the BI, were 61% (BI 95 to 100, good), 16% (BI 55 to 90, moderate), and 8% (BI 0 to 50, poor). The mortality rate was 15%. Over 2 years the median door-to-CT time decreased from 30 to 22 minutes (27%), and the door-to-needle time was shortened from 96 to 73 minutes (14%). The mean number of patients treated per month increased from 2 to 4.

Conclusions—Thrombolytic therapy can be performed safely and efficaciously in daily clinical routine. More than a minority of acute stroke patients might be eligible for intravenous thrombolysis. The performance of a stroke team can be improved over time, subsequently increasing the proportion of eligible patients and thereby the efficiency of the method. (Stroke. 2001;32:1074-1078.)

Key Words: outcome ■ stroke management ■ stroke, ischemic ■ thrombolytic therapy

Thrombolytic therapy with tissue plasminogen activator (tPA) has been shown to improve outcome in ischemic stroke patients treated within 3 hours from symptom onset. However, while the persuasive results of this study have launched some enthusiasm, safety concerns prevail among many clinical neurologists because of the risk of cerebral hemorrhage. Two large European studies and 2 trials from the United States have clearly shown that the time window for fibrinolytic therapy is rather narrow, although the results of the second European study suggest some benefit for patients who undergo thrombolysis, even when treated within 3 to 6 hours from symptom onset. Further concerns are nourished by a report from the “real world,” in which the translation of study results into daily clinical practice seemed to be less easy and more harmful than expected, despite the encouraging results of another multicenter survey. Furthermore, the small proportion of stroke patients suitable for thrombolytic treatment is another major point of criticism raised within the neurological community. Thus, time constraints and the logistic efforts required to offer thrombolysis to more than a minority of stroke patients have further limited the acceptance and wider use of thrombolysis in the daily routine of acute stroke care.

To prove whether the concept of systemic thrombolysis with tPA for ischemic stroke can be transferred into clinical practice, we prospectively assessed feasibility, safety, and efficacy in an academic medical center serving 500,000 residents in the south of Berlin, Germany. We further wanted to demonstrate that the performance of an acute stroke team can be improved within a decent period of time.

Received December 27, 2000; final revision received January 19, 2001; accepted January 22, 2001.

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Subjects and Methods

In May 1998, despite the (by this time) pending approval of tissue plasminogen activator (tPA) for the treatment of acute ischemic stroke in our country, we decided to offer thrombolytic therapy to patients with ischemic stroke. Programs to improve logistics and organization of acute stroke care were initiated: rescue teams of the Berlin Fire Department in the south of Berlin and staff at the emergency room were systemically trained to recognize candidates for thrombolytic therapy, and agreements were made with the departments of radiology and clinical chemistry to treat these patients with first priority. In addition, teaching courses were held at primary care hospitals in the south of Berlin to encourage transfer of patients suitable for thrombolytic therapy. The main criteria for thrombolytic therapy were adopted with some modification from the National Institute of Neurological Disorders and Stroke (NINDS) trial.1

Thus, alteplase (Actilyse; Boehringer Ingelheim) was administered in a dose of 0.9 mg/kg body weight (maximum dose 90 mg), with 10% given as a bolus followed by delivery of the remaining 90% as a constant infusion over a period of 60 minutes. Patients had to be treated within 3 hours from symptom onset; however, infringements of the 3-hour time window up to 4 hours in patients with a normal baseline CT scan were left to the discretion of the attending neurologists, who had to be present in all cases to finally decide and direct the acute treatment. NINDS study criteria were combined with the CT exclusion criteria of the European Cooperative Acute Stroke Study (ECASS) trials, ie, exclusion of patients with major early infarct signs in more than one third of the middle cerebral artery (MCA) territory.1,2 Because we included patients with strokes of the vertebrobasilar territory, patients with visible acute infarcts of the cerebellum (irrespective of the size) or the brain stem were also excluded. Pretreatment with aspirin or other antiplatelet agents was not an exclusion criterion. Special attention was paid to the control of elevated arterial blood pressure before, during, and for at least 24 hours after thrombolysis, according to the NINDS study criteria. Major logistic parameters (time from symptom onset to arrival at the emergency room [onset-to-ER time], door-to-CT time, door-to-needle time, onset-to-treatment time) were prospectively documented in all patients. The study was approved by the ethics committee of our hospital.

Neurological deficit on admission was measured by the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin scale (MRS). Eligible patients had to have a disabling neurological deficit independently from the NIHSS score at the time thrombolysis was started. Patients with rapidly improving symptoms were excluded. No upper age limit was defined; however, an MRS score of ≥3 before the acute event was an exclusion criterion. Informed consent was obtained from all patients or their next of kin. A follow-up CT scan was performed 24 hours after thrombolysis in all patients. The performance of further CT or MRI studies, as well as diagnostic studies to determine stroke etiology, were left to the discretion of the attending neurologists. Neither heparin nor aspirin, or other antiplatelet agents, were given for 24 hours after thrombolysis. Prespecified outcome parameters were the MRS and Barthel index (BI) at 3 months, and symptomatic hemorrhagic complications (ie, any intracranial hemorrhage leading to decline in neurological status,1 and any extracerebral hemorrhages requiring medical intervention like transfusion or surgery). A good outcome was defined as an MRS score of 0 or 1 or a BI of 95 to 100, a moderate outcome as an MRS score of 2 to 3 or a BI of 55 to 90, and a poor outcome as an MRS of 4 to 5 or a BI of 0 to 50. Follow-up data were obtained from structured telephone interviews 3 months after admission. Due to similar inclusion and exclusion criteria, late outcome parameters, the entire 24-month period was trisected into 8-month intervals (Table 2). Median door-to-CT, door-to-needle, and onset-to-treatment time intervals were decreased by 27%, 14%, and 13%, respectively, while the major patient-dependent parameter (ie, time from symptom onset to admittance) remained basically unchanged. During the 24 months of prospective data acquisition, the mean number of tPA-treated patients per month increased from 1.9 during months 1 to 8 to 4.1 during months 17 to 24, while the numbers of admitted stroke patients per month remained stable. Notably, door-to-CT and door-to-needle intervals showed a tendency to slightly increase from the second to the last 8-month interval (Table 2).

Parenchymal hemorrhage occurred in 2.7% of patients (n = 2) and was fatal in both cases. Neither of these patients was treated beyond 3 hours from onset, had an abnormal CT scan, or was pretreated with an antplatelet agent. However, protocol violations were evident in both cases: one patient was treated despite the fact that adjusted partial thromboplastin time was still elevated because of heparin given during cardiac catheterization; in the other patient, blood pressure was poorly controlled for 12 hours after treatment. In another patient, mild hemorrhagic transformation of an anterior cerebral artery infarct may have contributed to clinical worsening, but a definite causal association could not be determined due to the complexity of this case.11 Considering this case a hemorrhagic complication would increase the proportion of hemorrhages to 4%.

Early CT signs of acute cerebral infarction (hypointensification of cortical structures, sulcal effacement, insular ribbon hemorrhages to 4%.

Results

Between May 1998 and April 2000, a total of 802 patients with presumed stroke were admitted to our hospital, of whom 504 (62.8%) had suffered an ischemic cerebral infarction, as confirmed by brain scan or duration of symptoms of >24 hours. The remainder of diagnoses comprised 19% TIA (n = 152), 8.7% cerebral hemorrhages (n = 70), and 9.5% other diagnoses such as migraine, syncope, hypoglycemia, or seizure (n = 76). Of the patients with cerebral infarct, 32% (n = 161) arrived <3 hours after symptom onset, 8% (n = 40) were admitted after ≥3 but <6 hours, and 20% (n = 101) after ≥6 hours; in 40% (n = 202) the time of onset could not be determined, mostly due to onset of symptoms during the night or inconclusive statements about the time of onset.

Seventy-five patients were treated with intravenous tPA, which corresponded to 9.4% of all patients admitted for presumed stroke, 14.9% of patients with cerebral infarction, and 47% of those potentially eligible for thrombolytic treatment (ie, admitted within 3 hours from symptom onset). Main characteristics of tPA-treated patients are shown in Table 1. Twenty-five patients (33%) were taking antplatelet medication on admission. Median baseline NIHSS was 13, and thus similar to the NINDS trial.1 Ten patients (13.4%) were transferred from other hospitals. Thirteen patients (17.3%) were treated beyond 3 hours from symptom onset (mean 23, range 2 to 120 minutes). One aphasic patient was treated on the basis of her relative’s first statement regarding the time of onset, which was later markedly corrected backward; thus, thrombolytic had actually been started 300 minutes after onset. The infusion of tPA was prematurely stopped after 30 minutes in this patient.

To demonstrate the changes over time of major logistic parameters, the entire 24-month period was trisected into 8-month intervals (Table 2). Median door-to-CT, door-to-needle, and onset-to-treatment time intervals were decreased by 27%, 14%, and 13%, respectively, while the major patient-dependent parameter (ie, time from symptom onset to admittance) remained basically unchanged. During the 24 months of prospective data acquisition, the mean number of tPA-treated patients per month increased from 1.9 during months 1 to 8 to 4.1 during months 17 to 24, while the numbers of admitted stroke patients per month remained stable. Notably, door-to-CT and door-to-needle intervals showed a tendency to slightly increase from the second to the last 8-month interval (Table 2).

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A greater proportion (61% versus 45%) of patients achieved a good outcome, as assessed by the BI. However, because of the relatively small number of patients, the difference was not statistically significant ($\chi^2$ test, $P=0.07$). When the 8-month intervals were compared with regard to the proportion of patients with good functional outcome, no significant changes over time were detected for the MRS ($\chi^2$ test, $P=0.29$) or the BI ($\chi^2$ test, $P=0.55$).

### Discussion

Among clinical neurologists, thrombolysis for acute ischemic stroke remains a matter of debate despite quite encouraging results of large clinical trials, as well as phase IV experiences from single or multiple centers. In particular, the results from another phase IV study nourish concerns about unacceptably high complication rates of systemic thrombolysis when performed in the “real world.” However, the study from Cleveland is hardly comparable with our study and other phase IV studies, because of its retrospective design, the lack of documented stroke severity in the majority of patients, and the small number of thrombolized patients in most participating centers, indicating little experience with thrombolytic treatment. The low rate of symptomatic hemorrhages in the present study concurs with the results of other phase IV experiences and thereby confirms the assessment of outcome parameters after 3 months demonstrated that thrombolytic therapy was more efficacious than standard treatment (NINDS study placebo cohort) and that >70% of patients had a good or moderate outcome. Outcome results of the entire cohort in comparison with the NINDS trial, the ECASS I 3-hour IT population, and the results from Cologne are shown in Figure 1. Compared with the patients treated with tPA in the ECASS I 3-hour IT cohort (n=49), in our study a greater proportion (61% versus 45%) of patients achieved a good outcome, as assessed by the BI. However, because of the relatively small number of patients, the difference was not statistically significant ($\chi^2$ test, $P=0.07$). When the 8-month intervals were compared with regard to the proportion of patients with good functional outcome, no significant changes over time were detected for the MRS ($\chi^2$ test, $P=0.29$) or the BI ($\chi^2$ test, $P=0.55$).

### Table 1. Main Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NINDS rt-PA Trial, Part II (n=168)</th>
<th>Cologne (n=100)</th>
<th>Berlin (n=75)</th>
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<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>69±12</td>
<td>63±11</td>
<td>68±13 (34–90)</td>
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<tr>
<td>Gender, % male</td>
<td>60</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>Baseline NIHSS, median</td>
<td>14 (2–37)</td>
<td>12 (2–37)</td>
<td>13 (2–34)</td>
</tr>
<tr>
<td>Baseline MRS, median</td>
<td>NA</td>
<td>NA</td>
<td>4 (3–5)</td>
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<tr>
<td>Mean±SD time intervals, min</td>
<td>NA</td>
<td>NA</td>
<td>66±42 (14–263)</td>
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<td>Onset to hospital admittance</td>
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<td>NA</td>
<td>27±12 (2–61)</td>
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<td>Door to CT scan</td>
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<td>48±25 (20–130)</td>
<td>79±29 (25–150)</td>
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<tr>
<td>Door to needle</td>
<td>NA</td>
<td>124</td>
<td>144±41 (80–300)</td>
</tr>
<tr>
<td>Onset to treatment</td>
<td>NA</td>
<td>124</td>
<td>144±41 (80–300)</td>
</tr>
<tr>
<td>Time interval from onset to treatment, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤90 min</td>
<td>51</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>91–180 min</td>
<td>49</td>
<td>74</td>
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</tr>
<tr>
<td>&gt;180 min</td>
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</tr>
<tr>
<td>Stroke etiology, %*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac embolism</td>
<td>45</td>
<td>35</td>
<td>53</td>
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<tr>
<td>Artery-to-artery embolism</td>
<td>39</td>
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<td>8</td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>14</td>
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</tr>
<tr>
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<td>2</td>
<td>16</td>
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</tr>
<tr>
<td>Vascular territory, %</td>
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<tr>
<td>Carotid</td>
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<tr>
<td>Undetermined</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
</tr>
</tbody>
</table>

Numbers in parenthesis denote range. NA indicates not available.

*According to TOAST criteria.22
sumption that intravenous thrombolysis can be performed safely in daily clinical practice.

One other major point of criticism is the limited availability of thrombolysis for the vast majority of stroke victims. It is thus necessary to demonstrate that thrombolytic treatment can be implemented into the daily clinical routine of neurological stroke care by treating a decent proportion of acute stroke patients. However, the results as reported from phase IV evaluations are not always encouraging. In one study, it took almost 2 years and 57 medical centers to gather information about 389 consecutive patients treated with intravenous thrombolysis. Another retrospective study collected data from 13 hospitals over a 2-year period with 189 patients thrombolized; however, the total number of stroke patients and thus the proportion of treated subjects were not determined. In another survey of 29 hospitals, almost 4000 patients and thus the proportion of treated subjects were not determined. In summary, there is little evidence to prove that thrombolytic treatment is worth the effort to become part of routine stroke care. However, the results of the present study confirm the assumption that intravenous thrombolysis may not remain a therapy for a tiny minority of stroke patients.

Although the cost-effectiveness of tPA treatment has been proved, a specific proportion of successfully treated stroke patients is necessary to justify the technical, logistic, and financial efforts required for this treatment. Our study confirms the assumption that this goal is achievable with only moderate technical requirements and logistic efforts. We have further demonstrated for the first time that the performance of a stroke team can be improved over time, subsequently the proportion of thrombolized patients can be improved within a foreseeable period of time (Table 2). To date, information about specific time intervals in hyperacute stroke care are scarce. Reported door-to-CT times in thrombolized patients range from 33 to 41 minutes and are similar to our overall mean door-to-CT time of 27 minutes (Table 1). Wider ranges have been reported for the more important door-to-needle time. While 1 single center achieved an admirable mean of 48 minutes, the reported 94 minutes from another university hospital was similar to our 96 minutes during the first 8 months in our study. Recent analyses from the NINDS trial have demonstrated that even within the 3-hour time window, patients benefit most the earlier they are treated. Improving the performance of a stroke team is thus crucial to increase treatment efficacy. To the best of our knowledge, no data have been reported with respect to the evolution of logistic parameters over time in a stroke team. The increasing number of thrombolized patients over time in the present study indicates that improvement of hospital-dependent time parameters alone might additionally increase the proportion of patients eligible for thrombolysis. Given the difficulties in altering patient-related delays in stroke referrals, the implementation of an in-hospital fast track for acute stroke patients is even more important. However, we were not able to demonstrate changes in patient outcome with increasing experience of the stroke team. Indeed, the number of patients in our study is too small to reveal the presumably small effects on functional outcome over time.

In conclusion, the present study, which is one of the largest single-center experiences of thrombolysis for ischemic stroke according to established criteria, has demonstrated that systemic thrombolytic therapy can be implemented safely and efficaciously into daily clinical routine of stroke care. With some effort, thrombolysis may be a treatment option for more than a minority of patients with ischemic stroke. The performance of a stroke team can be improved over time, subsequently increasing the proportion of eligible patients.
Acknowledgments
This solely investigator-driven study was supported by an unrestricted grant from Boehringer Ingelheim. The authors thank the entire stroke unit staff of our department for their commitment. We are also grateful to the rescue teams of the Berlin Fire Department in the south of Berlin, the emergency room staff, and the personnel of the departments of Radiology and Clinical Chemistry at the Universitätsklinikum Benjamin Franklin.

References
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Stroke. 2001;32:1074-1078
doi: 10.1161/01.STR.32.5.1074

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