Pre- and In-Hospital Delays From Stroke Onset to Intra-arterial Thrombolysis

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Background and Purpose—Thrombolysis for treatment of acute ischemic stroke should be administered as fast as possible after symptom onset. The aim of this study was to examine, in our tertiary care center, the time intervals preceding intra-arterial thrombolysis in order to accelerate and optimize the management of acute strokes.

Methods—Between January 1, 2000, and April 30, 2002, 597 patients with acute stroke were admitted to our stroke center. One hundred forty-eight patients underwent diagnostic arteriography, and 100 (16.8%) received intra-arterial thrombolysis. For all patients, we prospectively recorded and analyzed the time of symptom onset, admission, CT and/or MRI scan, diagnostic arteriography, and, if performed, intra-arterial thrombolysis.

Results—The mean time to arrival in the emergency department was 99 minutes for patients who were admitted directly (Bern patients), 127 minutes for those who were referred from community hospitals without a CT scanner (non-Bern/CT patients), and 210 minutes for patients from hospitals with imaging facilities (non-Bern/CT patients). The mean delay from symptom onset to treatment was 234 minutes for Bern patients, 269 minutes for non-Bern/CT patients, and 302 minutes for non-Bern/CT patients. The patients from the last group needed longer to receive intra-arterial thrombolysis than did patients who were admitted directly (P=0.002) or who were transferred from a hospital without a CT scanner (P=0.03).

Conclusions—This prospective study indicates that direct referral without prior imaging at community hospitals shortens the time until intra-arterial thrombolysis. In addition, our in-hospital delay preceding intra-arterial thrombolysis is longer than the delays reported for intravenous thrombolysis and indicates potential for improvement. (Stroke. 2003;34:1230-1234.)

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

The National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study Group showed that intravenous recombinant tissue plasminogen activator (rtPA) is an efficacious treatment for acute ischemic stroke when given within 3 hours after stroke onset.1 Three large randomized trials, the first and second European Cooperative Acute Stroke Study (ECASS I and II) and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial, examined intravenous rtPA treatment beyond 3 hours. The intention-to-treat analyses failed to demonstrate a clear benefit.2-4 However, secondary analyses of the ECASS I and II data sets and a Cochrane meta-analysis suggest that rtPA is beneficial up to 6 hours after stroke onset but is less beneficial than within the 3-hour time window.5-7 Intra-arterial treatment with recombinant prourokinase improved clinical outcome significantly when administered up to 6 hours after stroke onset.8

Despite its proven efficacy, thrombolysis for treatment of acute ischemic stroke is underutilized, mostly because patients present too late at the hospitals offering this treatment. Another reason that patients are not given thrombolysis is the in-hospital delay.

To improve delivery of acute stroke therapy, some studies have analyzed the pre- and in-hospital process before intravenous thrombolysis.9-12 In this study we analyzed the time intervals preceding intra-arterial thrombolysis to optimize the logistics of acute stroke management in our center.

Subjects and Methods

Stroke Center and Catchment Area

The Inselspital is a tertiary care center and the main teaching hospital of the University of Bern, Bern, Switzerland. There is a mobile stroke team of staff neurologists and residents, neuroradiologists, neurosurgeons, and other specialists as needed. Intra-arterial thrombolysis was first performed at our institution in 1992 and since then has been applied more frequently every year. To enhance the use of thrombolysis, we performed continuing education on stroke medicine for laypersons and physicians in community hospitals and private offices.
Bern is the fourth largest city and the capital of Switzerland. There are 133,000 inhabitants in the city and 300,000 when the surroundings are included. Patients are referred mainly from the city area; however, the catchment area is larger and includes the whole canton of Bern and the surrounding cantons. For selected patients the catchment area of the Inselspital covers approximately 10,000 km² and serves >1,500,000 inhabitants. In the study period we received stroke patients from 57 community hospitals, 34 located within the canton of Bern and 23 located outside. Some community hospitals have CT and/or MRI scanners, but most lack intensive care facilities, and none perform thrombolysis for stroke. Distances from referring hospitals to the Inselspital vary from 2 to 130 km, and travel times range from a few minutes to up to 2 hours. Patients are transferred usually by ambulance and rarely by helicopter.

### Referral procedures and stroke workup

The Figure summarizes referral procedures and stroke investigations. When patients in Bern or the surrounding villages have symptoms that they recognize as harmful or threatening, they call the emergency medical system (EMS) or their family physician. If the symptoms are suggestive of acute ischemic stroke, the EMS or the family physician contacts the stroke team of the Inselspital and organizes the transfer to the emergency department (ED). On arrival at the ED, the neurologist on call performs an immediate clinical examination. An intravenous line and usually a urinary catheter are placed, blood is drawn, and a CT or, in selected patients, MRI scan is performed as soon as possible. After the CT or MRI scan is performed, the neurologist and interventional neuroradiologist decide jointly whether to perform angiography and eventually thrombolyis.

Patients who suffer their stroke onset outside of Bern and its surroundings are usually referred by EMS or by their family physician to the nearest community hospital. When possible, the initial CT examination and the laboratory assays of blood are performed in the community hospital. The decision to transfer patients to the Inselspital is made by the attending physician in the community hospital after consultation with our stroke team by telephone. Usually patients are transferred when the symptoms are suggestive of stroke, no clear contraindications for thrombolysis are present, eventual thrombolysis can be initiated at the Inselspital within 6 hours after symptom onset, and patients are aged <75 to 80 years. When patients from a community hospital arrive at the ED, they are admitted in the same way as patients from Bern. When patients have had a CT scan at the referring hospital, they proceed to angiography and thrombolysis directly from the ED when indicated.

### Intra-arterial Thrombolysis

Intra-arterial thrombolysis is performed if (1) diagnosis of ischemic stroke is established; (2) baseline National Institutes of Health Stroke Scale (NIHSS) score is ≥4 points, except for isolated hemianopia and aphasia; (3) time of symptom onset is clearly defined; (4) treatment can be initiated within 6 hours from symptom onset; (5) the patient is aged ≥80 years; and (6) the patient or his/her next of kin consents to arteriography and potential thrombolysis. Two patients who were older than 80 years and in excellent general health before the onset of stroke symptoms underwent thrombolysis despite the age limit. These criteria are similar to those used in the PROlyse in Acute Cerebral Thromboembolism trial (PROACT II) for all stroke localizations except for basilar artery occlusion. When clinical symptoms and signs are suggestive of basilar artery thrombosis, arteriography and thrombolysis are attempted beyond the 6-hour time window when the patient has not been in a coma for a prolonged period or when diffusion and perfusion MRI do not advise against thrombolysis. Patients undergo 4-vessel diagnostic cerebral arteriography and thrombolysis is performed when an occluded vessel explaining the clinical deficit is found. Details of the angiographic procedure and the process of delivery of the thrombolytic agent have been described previously. We use urokinase (Urokinase HS Medac) in a dose ranging from 500,000 to 1,250,000 IU, which is infused over 60 to 90 minutes. Treatment effect is documented by a control arteriography immediately after administration of urokinase. After thrombolysis, all patients receive 250 to 500 mg aspirin. Control CT scan or MRI is routinely performed within 24 hours after intra-arterial thrombolysis or any time in case of neurological deterioration.

### Data Collection and Statistical Analysis

All acute stroke patients seen at the Inselspital from January 1, 2000, to April 30, 2002, who underwent diagnostic arteriography were included in this study. All the data used for this analysis were collected prospectively. Demographic variables, cerebrovascular risk factors, personal history for previous cerebrovascular events, time of symptom onset, pretreatment time intervals, NIHSS scores at admission, stroke workup, treatment, and outcome as measured by the modified Rankin Scale (mRS) at 3 months were entered into a stroke data bank. Time of symptom onset was considered the moment that the patient indicated in his history. In aphasic or comatose patients or when stroke occurred during sleep, the time when the patient was last seen to be well was presumed to be the time of onset. Time of arrival at ED of the Inselspital was noted in the ED record. Time of CT scan, MRI scan, and arteriography was printed on the films, and the time of thrombolysis was recorded on the angiographic films as well as in the neuroradiology report. The following time intervals were analyzed: (1) time from symptom onset to arrival in the Inselspital (onset to door); (2) time from symptom onset to CT or MRI scan performed in the Inselspital or in a community hospital (onset to CT scan); (3) time from symptom onset to arteriography (onset to arteriography); (4) time from arrival to arteriography (door to arteriography); and (5) time from symptom onset to thrombolysis (onset to treatment). Travel distances and travel times were calculated with the use of a Web-based route planner (WEB.DE Routeplaner). For analysis, patients were stratified into 3 groups: (1) patients referred directly to the Inselspital (Bern patients); (2) patients transferred from a community hospital without a CT scan (non-Bern/−CT patients); and (3) patients transferred from a community hospital with a CT scan (non-Bern/+ CT patients).

Statistical analysis was performed with SPSS 10 for MacIntosh statistical software (2001; SPSS Inc). Demographic data, time intervals, and other descriptive statistics are given as mean values and SDs, except for NIHSS scores, which are given as median values. The Mann-Whitney test was used to compare the time intervals between patient groups. The effect of demographic factors, travel distances, stroke severity, and arrival during or out of regular
working hours on time intervals was analyzed with Spearman’s ρ test. Probability values of P<0.05 were considered significant.

Results

Demographics and Baseline Characteristics

During the study period, 597 patients with acute ischemic stroke were seen by our stroke team. One hundred forty-eight patients (24.8%) underwent arteriography, and 100 (16.8%) received intra-arterial thrombolysis with the use of urokinase. In 48 patients thrombolysis was not performed for the following reasons: (1) occlusion of an extracranial cerebral artery prevented access to the occluded intracranial vessel (n=25 patients); (2) no vessel was seen to be occluded on arteriography (n=21); and (3) aortic dissection was present (n=2). Seventy-three patients (49.3%) were admitted directly after a CT scan in a community hospital (non-Bern/CT patients); (2) no vessel was seen to be occluded on arteriography (n=21); and (3) aortic dissection was present (n=2). Seventy-three patients (49.3%) were admitted directly from a community hospital without a CT scan (non-Bern/CT patients). One hundred forty-eight patients (24.8%) underwent arteriography, and 100 (16.8%) received intra-arterial thrombolysis with the use of urokinase.

Demographic data and baseline characteristics are shown in Table 1. Demographic data and baseline characteristics are shown in Table 1.

Time to Arrival at ED of Inselspital

Mean pre- and in-hospital time intervals before treatment are given in Table 2. Mean onset-to-door times differed significantly among the 3 patients groups. Bern patients presented to the ED of the Inselspital 99±63 minutes (median, 85 minutes) after symptom onset, non-Bern/−CT patients arrived after 127±56 minutes (median, 135 minutes), and non-Bern/+CT patients arrived after 210±66 minutes (median, 210 minutes).

The mean travel distances were 25±25 km for Bern patients, 40±33 km for non-Bern/−CT patients, and 80±51 km for non-Bern/+CT patients. Travel distances of Bern patients were significantly shorter than those of non-Bern/−CT patients (P=0.02) and non-Bern/+CT patients (P<0.0001). Travel distances of non-Bern/+CT patients were also longer than those of non-Bern/−CT patients (P<0.0001).

There was a strong correlation between the travel distance and the onset-to-door time for non-Bern/+CT patients (Spearman’s ρ=0.52; P<0.001) but not for Bern or non-Bern/−CT patients.

After adjustment for travel distances, ie, deduction of the travel times as indicated in the WEB.DE route planner from the onset-to-door times, Bern patients and non-Bern/−CT patients arrived faster than non-Bern/+CT patients (P<0.0001). There was no difference between Bern patients and non-Bern/−CT patients.

Times to Stroke Workup and Treatment

The onset-to-arteriography, door-to-arteriography, and onset-to-treatment times are given in Table 2. The differences of onset-to-arteriography times remained after adjustment for travel distances (P<0.001). There was no difference between Bern and non-Bern/−CT patients.

There was an inverse relationship between onset-to-door and door-to-arteriography times for both Bern and non-Bern patients (Spearman’s ρ=−0.46; P<0.001).

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Bern Patients</th>
<th>Non-Bern/−CT</th>
<th>Non-Bern/+CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>73</td>
<td>24</td>
<td>51</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>62 (13)</td>
<td>60 (13)</td>
<td>60 (11)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>34 (47)</td>
<td>12 (50)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>History of, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (44)</td>
<td>12 (50)</td>
<td>24 (46)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (10)</td>
<td>2 (8)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (25)</td>
<td>8 (30)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17 (23)</td>
<td>9 (38)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>10 (14)</td>
<td>4 (17)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>NIHSS score at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Patients treated with IAT, n (%)</td>
<td>49 (67)</td>
<td>10 (42)</td>
<td>41 (60)</td>
</tr>
</tbody>
</table>

IAT indicates intra-arterial thrombolysis.

<table>
<thead>
<tr>
<th>Time Interval, Min (SD)</th>
<th>Bern</th>
<th>Non-Bern/−CT</th>
<th>Non-Bern/+CT</th>
<th>P†</th>
<th>P‡</th>
<th>P§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset-to-door</td>
<td>99 (63)</td>
<td>127 (56)</td>
<td>210 (66)</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset-to-CT</td>
<td>116 (57)</td>
<td>166 (50)</td>
<td>129 (65)</td>
<td>0.02</td>
<td>NS</td>
<td>0.04</td>
</tr>
<tr>
<td>Onset-to-arteriography</td>
<td>198 (83)</td>
<td>229 (44)</td>
<td>277 (53)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door-to-arteriography</td>
<td>109 (67)</td>
<td>92 (45)</td>
<td>66 (41)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Onset-to-treatment</td>
<td>234 (68)</td>
<td>269 (42)</td>
<td>302 (55)</td>
<td>NS</td>
<td>0.002</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Bern patients were admitted directly to the Inselspital. Non-Bern/−CT patients were referred from a community hospital without a CT scan. Non-Bern/+CT patients were referred from a community hospital after CT examination.
†Comparison of Bern patients and non-Bern/−CT patients;
‡Comparison of Bern patients and non-Bern/+CT patients;
§Comparison of non-Bern/−CT patients and non-Bern/+CT patients.
Sex, age, time of symptom onset during day or night, arrival at the Inselspital or a community hospital during or out of regular working hours, history of previous cerebrovascular events, stroke localization, and NIHSS score on admission had no influence on any of the time intervals before treatment.

Discussion
Intravenous and intra-arterial thrombolysis can be safely administered in single stroke centers, achieving results comparable to those of the randomized trials.12,14,17–21 It has also been shown that educational programs for both the public and physicians increase the number of patients arriving at the hospitals within the time limits for thrombolysis.22 In US stroke centers, up to 59% of the patients who presented within 24 hours of symptom onset arrived within 3 hours.23–25 In countries such as the United Kingdom or Ireland, where tPA has not been approved for stroke treatment and systematic educational programs have not been performed, longer onset-to-arrival delays have been reported.26 However, a third of the patients arrived within 3 hours and nearly half arrived within 6 hours of symptom onset. These data show that it may be realistic for a substantial proportion of stroke patients to receive intravenous or intra-arterial thrombolysis. When the numbers of patients who receive thrombolysis are considered, the figures are not as impressive. Only 9% to 22% of the patients receive intravenous thrombolysis.19,17 In the present series 16.8% received intra-arterial thrombolysis. We must consider how to further increase the number of patients treated.

Since time is critical in performing thrombolysis, in this study we analyzed the time intervals preceding treatment. The time intervals depend mainly on the regional organization of a healthcare system, geographic characteristics, patient and physician awareness of stroke symptoms, referral pathways, and in-hospital factors. In our institution thrombolysis is delivered almost exclusively with the use of selective arteriography and intra-arterial urokinase within a 6-hour time window. Therefore, this study represents an analysis of time intervals before intra-arterial thrombolysis. Similar analyses have already been performed for intravenous treatment.17–20,27

Patients who were transferred directly to our stroke center were mostly residents of Bern or an area close to that vicinity. Their mean prehospital delay was 99 minutes. When patients were first referred to a community hospital and then forwarded to our institution after clinical examination but without neuroradiological evaluation, their onset-to-door time was lengthened by the travel time. However, when the onset-to-door times are adjusted for the travel distance, there was no difference for the patients admitted directly or referred from a community hospital. This means that the community hospital staffs were acting very rapidly.

Patients living farther away from the Inselspital were more likely to have a CT scan at the community hospital. This CT scan in the community hospital was initiated as fast as CTs for patients referred directly to the Inselspital, but it added a significant delay to the onset-to-door time to the Inselspital. This additional delay was compensated in part but not entirely by shorter door-to-arteriography and door-to-
treatment times at the Inselspital. The decision to transfer a stroke patient seems to be shorter in the hospitals without CT scanning capabilities. This may indicate that performing and interpreting a CT scan in the community hospital complicates the process of stroke treatment. It involves additional people in the community hospital and is more time-consuming than when imaging is performed by the stroke team that also performs the thrombolysis. The results suggest that patients presenting to a community hospital with a clinical picture suggestive of acute stroke should be sent to the closest referral center without undergoing a CT scan. However, a drawback of such a policy may be a potential overload of the referral center with patients who after CT are found to have a contraindication for thrombolysis or other special treatments. There was an inverse relationship between onset-to-door and door-to-arteriography times. This finding may indicate that in-hospital delays can be shortened when the 6-hour deadline approaches. This phenomenon has also been observed in intravenous tPA studies when the 3-hour limit was close.18,28

Demographic factors such as sex and age did not influence the time delay to treatment. Patients who were already familiar with the signs and symptoms of stroke because of previous cerebrovascular events did not arrive faster in the ED of our stroke center. Strokes that were localized in the territory of the carotid arteries were not recognized earlier than strokes that occurred in the vertebrobasilar territory. Stroke severity had no influence on the time delay preceding treatment. Arrival within or out of regular working hours did not affect pre- and in-hospital time intervals.

To summarize, this study shows that direct referral of stroke patients from a community hospital without prior imaging shortens onset-to-treatment time. In addition, in-hospital delays were shorter when the deadline for treatment was approaching. This may indicate that there is also a potential to decrease the in-hospital time intervals when the deadline for thrombolysis is more distant.

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References


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