Long-Term Effect of Intra-Arterial Thrombolysis in Stroke

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Background and Purpose—Thrombolysis has been shown to improve the 3-month outcome of patients with ischemic stroke, but knowledge of the long-term effect of thrombolysis is limited.

Methods—The present study compares the long-term outcome of stroke patients who were treated with intra-arterial thrombolysis (IAT) using urokinase with the outcome of patients treated with aspirin. The modified Rankin Scale (mRS) was used to assess the outcome; 173 patients treated with IAT and 261 patients treated with aspirin from the Bernese Stroke Data Bank were eligible for the study. A matching algorithm taking into account patient age and stroke severity on admission (as measured by the National Institute of Health Stroke Scale [NIHSS]) was used to assemble an IAT and an aspirin group.

Results—One hundred and forty-four patients treated with IAT and 147 patients treated with aspirin could be matched and included in the comparative analysis. The median NIHSS score was 14 in each group. At 2 years, 56% of the patients treated with IAT and 42% of the patients treated with aspirin achieved functional independence (mRS, 0 to 2; P=0.037). Clinical outcome was excellent (mRS, 0 to 1) in 40% of the IAT and in 24% of the aspirin patients (P=0.008). Mortality was 23% and 24%, respectively.

Conclusions—The present study provides evidence for a sustained effect of IAT when assessed 2 years after the stroke.

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Key Words: intra-arterial thrombolysis ■ long-term outcome ■ stroke ■ urokinase

Several randomized and observational studies found that thrombolytic therapy can improve the 3-month outcome of patients with acute ischemic stroke.1-12 Few studies reported sustained effects of intravenous thrombolysis at 6 to 12 months after stroke onset.10,13-16 Until now, it was not known whether intra-arterial thrombolysis (IAT) would also exert long-standing benefits after stroke.

The present study tested the hypothesis that the effect of IAT is durable and would persist beyond the usual follow-up of 3 months. For this reason, we compared the long-term outcome of stroke patients treated with IAT with that of patients treated with aspirin within the first 24 hours after symptom onset.

Materials and Methods

This study is based on the Bernese Stroke Data Bank, which is a systematic prospective registry of consecutive patients with ischemic stroke admitted to the Inselspital, a university-based stroke center in Switzerland. From January 2000 to June 2004, data of 743 consecutive patients with a final diagnosis of acute ischemic stroke or transient ischemic attack (TIA) were entered into the data bank. Stroke was diagnosed by a neurologist. The diagnosis was based on a focal neurological deficit that lasted for at least 24 hours with or without corresponding ischemic lesions on brain imaging.17 The TOAST classification (trial of ORG 10172 in acute stroke treatment) was used to define the etiology of stroke: (1) large artery atherosclerosis; (2) cardioembolism; (3) small vessel disease; (4) stroke of other determined etiology; and (5) stroke of undetermined etiology.18

The following stroke risk factors were assessed: sex, hypertension (defined by preadmission history and medical records), diabetes mellitus (defined by venous plasma glucose concentration of ≥7.0 mmol/L after an overnight fast on at least 2 separate occasions, and/or ≥11.1 mmol/L 2 hours after the ingestion of 75 grams of oral glucose and on one other occasion during the 2-hour test), current cigarette smoking, hypercholesterolemia (defined as total venous plasma cholesterol concentration >5 mmol/L), heart disease, history of amaurosis fugax (monocular blindness lasting <24 hours), retinal infarction (monocular blindness lasting ≥24 hours), TIA (neurological deficit lasting <24 hours), or ischemic stroke.

The severity of the neurological deficit on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).19

Patients admitted within 6 hours from stroke onset were considered candidates for thrombolytic therapy (intravenous or intraarterial). They underwent either a perfusion CT assessment and CT angiography or MRI including diffusion-weighted and perfusion-weighted imaging and first-pass Gd-DTPA–enhanced magnetic resonance angiography. Patients with proximal cerebral artery occlusions (ie, internal carotid artery, M1 or M2 segment of the middle cerebral artery, A1 segment of the anterior cerebral artery, basilar artery, P1 segment of the posterior cerebral artery) are treated with IAT at our institution, even if they present within 3 hours from symptom onset.
Patients admitted within 3 to 6 hours from stroke onset are also treated with IAT.

IAT was performed if: (1) diagnosis of ischemic stroke was established; (2) baseline NIHSS score was ≥4 points, except for isolated hemianopia and aphasia; (3) time of symptom onset was clearly defined; (4) treatment could be initiated within 6 hours from symptom onset; and (5) the patient or next of kin consented to arteriography and potential thrombolysis. When clinical symptoms and signs were suggestive of basilar artery thrombosis, arteriography and thrombolysis were attempted beyond the 6-hour time window when the patient had not been in a coma for a prolonged period and MRI including diffusion-weighted and perfusion-weighted images did not advise against thrombolysis. Patients underwent 4-vessel diagnostic cerebral arteriography followed by local infusion of 500 000 to 1 250 000 IU urokinase (Urokinase HS Medac) over 60 to 90 minutes. Whenever possible, mechanical thrombus retrieval using thrombus aspiration was performed in addition to the urokinase infusion. Treatment effect was documented by a control arteriography immediately after administration of urokinase.

Patients who did not meet the criteria for thrombolysis were given 250 mg to 500 mg aspirin immediately after exclusion of intracranial hemorrhage by neuroimaging. Control CT scan or MRI was routinely performed within 24 hours after IAT or in case of neurological deterioration.

Aspirin (100 mg to 300 mg), clopidogrel (75 mg), or anticoagulation were used for secondary prevention of stroke according to widely accepted guidelines.20

The clinical outcome was evaluated using the modified Rankin scale (mRS) score.21 The following definitions of favorable outcome were used: (1) excellent outcome (mRS 0 or 1) and (2) functional independence (mRS 0 to 2). Neurologists or physicians in neurology training certified for NIHSS and mRS assessment performed the follow-up. They were not blinded to treatment.

In patients treated with IAT, outcome was assessed at 3 months (early clinical outcome) and 24±18 months after the ictus (long-term clinical outcome). Early clinical outcome was assessed during a follow-up visit at the hospital; long-term outcome was evaluated either during follow-up visits or by structured telephone interviews. Patients treated with aspirin were not examined systematically at 3 months after the ictus. Their long-term outcome was assessed at 23±22 months after stroke onset.

Matching Algorithm
Patients treated with IAT (n=173) and those having no contraindications for IAT other than delayed presentation at the stroke center (n=261) were eligible for the study. Patients who presented at the stroke center later than 24 hours after symptom onset were not considered for this study.

Stratified random matching that took into account patient age and NIHSS score on admission was used to assemble an IAT and an aspirin group (Table 1). All patients were plotted against their NIHSS score and then allocated to the following 4 strata: (1) NIHSS score 5; (2) NIHSS score 6 to 8; (3) NIHSS score 9 to 18; and (4) NIHSS score >18. The cutoffs were chosen empirically to provide an adequate number of both patients treated with IAT and aspirin in each stratum. In the first stratum, there were 3 patients treated with IAT and 47 patients treated with aspirin (Table 1). Of the latter group, 3 patients were

<table>
<thead>
<tr>
<th>NIHSS score 5</th>
<th>IAT group</th>
<th>Non–IAT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score 6 to 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score 9 to 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score &gt;18</td>
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</tbody>
</table>

† Eligible for the study; †† included in the study
randomly chosen to match the age of the IAT patients. In the second stratum, 20 age-matched patients treated with IAT were randomly selected among the 90 aspirin patients. All the patients from the third stratum were included in the study. There were 57 IAT and 28 aspirin patients in the fourth stratum. Of the 57 IAT patients, 28 patients were selected to match the age of the 28 patients treated with aspirin.

Matching was blinded for clinical outcome. One hundred forty-four patients treated with IAT (mean age 63 years, 51% women) and 147 patients treated with aspirin (mean age 62 years, 37% women) were included in the comparative analysis. The median NIHSS was 14 in each group.

Statistical Analysis
Quantitative data are expressed as mean values ± standard deviation. The NIHSS score for each patient at admission is given as a median value. Differences between groups and the effect of patient characteristics (ie, sex, cause of stroke, vascular risk factors, blood glucose on admission, history of cerebrovascular ischemic events, and territory of the occluded artery) on clinical outcome were assessed with the χ² test. The Mann-Whitney test was used to assess the effects of age and initial stroke severity on the clinical outcome. A logistic regression analysis, which included variables that showed statistical difference \( P<0.2 \) on univariate comparison, was performed.

Results
Demographic data, prevalence of vascular risk factors, blood glucose on admission, stroke etiology, severity, and distribution in the carotid or the vertebrobasilar territory are shown in Table 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IAT</th>
<th>Aspirin</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>63 (12)</td>
<td>62 (14)</td>
<td>0.016</td>
</tr>
<tr>
<td>Female sex</td>
<td>51%</td>
<td>37%</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose on admission, mmol/L (SD)</td>
<td>7.35 (2.5)</td>
<td>7.32 (2.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13%</td>
<td>14%</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking</td>
<td>26%</td>
<td>19%</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>42%</td>
<td>41%</td>
<td>NS</td>
</tr>
<tr>
<td>Median NIHSS score</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>26%</td>
<td>15%</td>
<td>0.017</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>21%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>3%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>20%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>29%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke localization</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Carotid artery territory</td>
<td>93%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Vertebrobasilar territory</td>
<td>7%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

Both groups were matched for age and stroke severity on admission. The proportion of women was significantly higher among the patients treated with IAT (51%) than in the aspirin group (37%, \( P=0.016 \)). The prevalence of vascular risk factors and the blood glucose on admission did not differ between the groups. Strokes caused by large artery atherosclerosis or other determined etiology were more prevalent in the IAT group (26% versus 15%, \( P=0.017 \), and 20% versus 6%, \( P<0.001 \), respectively), whereas cardioembolic strokes were more common in the aspirin group (49% versus 21%; \( P<0.001 \)). The prevalence of vertebrobasilar strokes was significantly higher in the aspirin compared with the IAT group (19% versus 7%, \( P=0.002 \)).

Early clinical outcome was assessed only in the IAT group. Thirty-one percent of the patients had excellent outcomes (mRS, 0 or 1) at 3 months after stroke onset (Figure 1a). This proportion increased to 40% when assessed 24 ± 18 months after the ictus. The proportion of patients with functional independence (mRS, 0 to 2) was 56% at both early and long-term outcome assessment (Figure 1b).

Long-term outcome was assessed in both groups. Two patients treated with IAT and 8 patients treated with aspirin were lost to follow-up. Applying the intention-to-treat principle, they were included in the analysis as having an adverse outcome. At long-term outcome assessment, 40% of the IAT and 24% of the aspirin patients had an excellent outcome (\( P=0.008 \)) (Figure 2). The proportion of patients with functional independence was 56% and 42%, respectively, in the
IAT and the aspirin group ($P=0.037$). Mortality was 23% in the IAT and 24%, respectively.

Sex, stroke etiology, blood glucose on admission, and localization in the carotid or the vertebrobasilar territory were not associated with the clinical outcome in the univariate or in the logistic regression analysis.

Logistic regression analysis showed that a high NIHSS score on admission and hypertension were independent predictors of adverse outcome in patients treated with aspirin ($P=0.002$, $P=0.009$, when adverse outcome was defined as mRS 2 to 6; and $P<0.001$, $P<0.001$, when adverse outcome was defined as mRS 3 to 6). Independent predictors of adverse outcome in patients treated with IAT were a high NIHSS score on admission and advancing age ($P<0.001$ and $P=0.003$, when adverse outcome was defined as mRS 2 to 6; and $P<0.001$ and $P<0.001$, when adverse outcome was defined as mRS 3 to 6).

**Discussion**

The present study compares the long-term outcome of patients treated with IAT and patients treated with aspirin in the acute phase of stroke. Both groups were selected among 743 consecutive patients with ischemic stroke admitted to our university-based stroke center over a period of 4.5 years. Delayed presentation at the stroke center was the only reason to withhold thrombolysis in the group treated with aspirin.

The main finding of our study was a sustained effect of IAT over a mean follow-up period of 2 years after the stroke. Patients treated with IAT were more likely to have excellent outcomes (16% absolute difference, $P=0.008$) or functional independence (14% absolute difference, $P=0.037$) than patients treated with aspirin.

Both groups were matched for age and NIHSS score on admission. Several studies have shown that age and NIHSS score on admission are powerful predictors of outcome in patients with ischemic stroke.22 Previous studies of our group and a most recent analysis found age, stroke severity on admission, diabetes mellitus, good leptomeningeal collaterals, time from symptoms onset to thrombolysis, successful recanalization, and symptomatic intracranial hemorrhages to be independently associated with outcome in patients treated with IAT.7,12,23–25 Age, stroke severity, diabetes mellitus, and leptomeningeal collaterals are patient-related predictors. They may introduce bias into the comparative analysis, if they are unevenly prevalent in the IAT and the aspirin groups. The remaining factors depend mostly on thrombolysis (treatment-related predictors) and need no further adjustment.

In this study, NIHSS score on admission was the most robust predictor of long-term disability. Hypertension was an independent predictor of unfavorable outcome in patients receiving aspirin, increasing age-predicted disability in patients treated with IAT. Stroke severity, age, and hypertension were well balanced between the groups.

There were inevitable differences in other baseline characteristics such as sex, large artery atherosclerosis, cardioembolism, and localization in the carotid or the vertebrobasilar territory (Table 2). A pooled analysis of randomized clinical trials suggests that women achieve more favorable outcome than men after intravenous thrombolysis for ischemic stroke.26 If this holds true also for IAT, the higher prevalence of women in the IAT group would be to the advantage of the thrombolytic treatment. Large artery atherosclerosis appears to be a powerful predictor of early recurrent stroke (within 30 days after stroke), but it does not predict functional outcome.22 Compared with other stroke subtypes, cardioembolic stroke, which was twice that prevalent in the aspirin group of our study, was associated with a less favorable outcome in a population-based study of all residents of Rochester, Minnesota.27 According to a recent multinational hospital-based study, patients with territorial infarcts in the anterior circulation were those with the highest level of disability at 3 months, followed by patients with lacunar and vertebrobasilar strokes.28 Matching for all these variables and other possible confounders would result in considerable methodological improvement. However, it would have excluded too many patients and lead to loss of statistical power.

Excellent outcome after stroke is traditionally defined as complete recovery or no significant disability despite symptoms (mRS, 0 to 1). At 3 months, improving to mRS 2 is usually considered a favorable outcome, because a patient may have a slight disability but he or she is able to look after own affairs without assistance (mRS, 2). However, achieving mRS 2 in the long-term might be perceived as unsatisfactory, especially by patients with moderate initial neurologic deficits (NIHSS ≤7).16 Furthermore, the major randomized thrombolysis trials used different definitions of favorable outcome (mRS 0 or 1 in the NINDS rt-PA stroke study, mRS 0 to 2 in the PROACT II study).1,2 Therefore, we used both definitions in our analysis.

There are few long-term outcome reports after intravenous recombinant tissue plasminogen activator (rt-PA) treatment and, apart from the NINDS rt-PA study, none of the studies was a randomized trial or had a control group in any other nonrandomized form. Figure 3 shows data that are only descriptive and can at most give rise to an indirect noncontrolled comparison. The 40% excellent outcome (Figure 3a) and 56% functional independence (Figure 3b) at 2 years in our study are similar to previous studies using intravenous rt-PA (Figure 3a).10,13,15,16 The percentage of favorable outcomes is also in the range of the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST).29 However, IAT can safely be administered within 3 to 6 hours after symptom onset, when intravenous thrombolysis is an option for selected patients, mostly based on pretreatment MRI.30,31

Our study has some limitations. First, we did not assess systematically the outcome in patients treated with aspirin at 3 months. Therefore, we have no data to compare the outcome in both groups at this time point. Nevertheless, the NINDS rt-PA study showed that the beneficial effect of thrombolysis observed at 3 months remained stable over the subsequent 9 months.15 Therefore, we believe that our IAT and aspirin patients would have shown a difference in the same order as after 2 years, if we had not missed the opportunity to assess the aspirin patients at 3 months. Second, the time points at which long-term outcome was assessed
However, strong evidence of a durable effect of IAT for study and observational intravenous thrombolysis trials. comparable to that of patients treated in the NINDS rt-PA. Long-term outcome in stroke patients treated with IAT is number of potential confounders (both known and unknown) that could have influenced the study results. Nevertheless, the large sample size and the blinding for outcome when assembling both groups would counteract at least in part the effect of such confounders.

To summarize, the present study demonstrates a sustained effect of IAT when assessed 2 years after the stroke. The long-term outcome in stroke patients treated with IAT is comparable to that of patients treated in the NINDS rt-PA study and observational intravenous thrombolysis trials. However, strong evidence of a durable effect of IAT for treatment of ischemic stroke can be provided only by a randomized controlled trial.

Disclosures

None.

References


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