Early Recurrent Ischemic Stroke in Stroke Patients Undergoing Intravenous Thrombolysis

Dimitrios Georgiadis, MD; Stefan Engelter, MD; Barbara Tettenborn, MD; Hansjörg Hungerbühler, MD; Regina Luethy, MD; Felix Müller, MD; Marcel Arnold, MD; Christian Giambarba, MD; Christian Rainer Baumann, MD; Hans-Christian von Büdingen, MD; Philipp Lyrer, MD; Ralf Werner Baumgartner, MD

Background—We assessed the incidence of early recurrent ischemic stroke in stroke patients treated with intravenous tissue-type plasminogen activator (tPA) and the temporal pattern of its occurrence compared with symptomatic intracranial hemorrhage (ICH).

Methods and Results—Prospectively collected, population-based data for 341 consecutive acute stroke patients (62% men; mean age, 66 years) treated with tPA according to the National Institute of Neurological Disorders and Stroke study protocol at 8 medical centers in Switzerland (3 academic and 5 community) between January 2001 and November 2004 were retrospectively analyzed. The primary outcome measure was neurological deterioration ≥4 points on the National Institutes of Health Stroke Scale occurring within 24 hours of tPA treatment and caused either by recurrent ischemic stroke (defined as the occurrence of new neurological symptoms suggesting involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on cranial computed tomography scans, in the absence of ICH) or by ICH. Early recurrent ischemic stroke was diagnosed in 2 patients (0.59%; 95% confidence interval, 0.07% to 2.10%) and symptomatic ICH in 15 patients (4.40%; 95% confidence interval, 2.48% to 7.15%). Both recurrent ischemic strokes occurred during thrombolysis, whereas symptomatic ICHs occurred 2 to 22 hours after termination of tPA infusion.

Conclusions—Recurrent ischemic stroke is a rare cause of early neurological deterioration in acute stroke patients undergoing intravenous thrombolysis, with a different temporal pattern compared with that of symptomatic ICH.

Key Words: cerebral infarction ■ cerebral ischemia ■ cerebrovascular disorders ■ stroke ■ thrombolysis

Thrombolysis for acute myocardial infarction initially raised concerns that the disintegration of potentially preexisting cardiac thrombus could lead to systemic (and in particular, cerebral) embolism.1 It appears plausible that the same mechanism could apply to patients with cardiac or arterial thrombi who are undergoing intravenous thrombolysis (IVT) for acute ischemic stroke, constituting a further cause of neurological deterioration besides intracranial hemorrhage (ICH) and progressive ischemic stroke.

Considering the pharmacodynamic properties of tissue-type plasminogen activator (tPA; half-life of 5 minutes, with only 6.25% of the initial concentration present in plasma 20 minutes after termination of infusion), recurrent ischemic stroke due to tPA should occur early, ie, during or within the first hours after IVT (thus designated as early recurrent ischemic stroke [ERIS] in this study). ICH, on the other hand,

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would be expected to present a different temporal pattern, as fibrinogen levels only return to normal (within 80% of the initial value) 24 hours after IVT.2 Symptomatic ICH (SICH) was reported in 20 patients treated with tPA in the National Institute of Neurological Disorders and Stroke (NINDS) trial and occurred 2 to 29 hours after IVT initiation; in 95% of cases, symptoms occurred within the first 24 hours.2

Recurrent ischemic stroke constituted an end point in the NINDS rt-PA Stroke Study3 but not in the European Cooperative Acute Stroke Study (ECASS) I,4 ECASS II,5 or Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS)6 trials or the Standard Treatment with Alteplase to Reverse Stroke (STARS)7 Study.
Even in the NINDS trial, recurrent ischemic stroke was reported for the whole follow-up period of 90 days, but specific details about the time point of its occurrence were not provided, making it impossible to differentiate between ERIS and recurrent ischemic stroke due to other causes.

This retrospective, population-based study collected data from all centers of German-speaking Switzerland that perform IVT for acute ischemic stroke to investigate the incidence and time of onset of ERIS and SICH within the first 24 hours after intravenous tPA, administered according to the NINDS study protocol during an observation period of 47 months.

Methods

We hypothesized that ERIS associated with IVT should occur during or within hours after termination of tPA infusion. Surveillance for ERIS or SICH was limited to 24 hours after IVT, a time window also adopted by the PROlyse in Acute Cerebral Thromboembolism (PROACT) trial. We hypothesized that ERIS associated with IVT should occur during or within hours after termination of tPA infusion. Surveillance for ERIS or SICH was limited to 24 hours after IVT, a time window also adopted by the PROlyse in Acute Cerebral Thromboembolism (PROACT) trial.8

Patients with neurological deterioration causing a ≥4-point worsening on the National Institutes of Health Stroke Scale (NIHSS) were further evaluated. ERIS was defined as the occurrence of new neurological symptoms suggesting the involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on cranial computed tomography (CCT) scans, in the absence of ICH. Neurological deterioration and evidence of appropriately located ICH on CCT, magnetic resonance imaging (MRI) scans, or both was diagnosed as SICH.

Data collected included patient age, sex, NIHSS score on admission, latency between symptom onset and initiation of IVT, and latency between initiation of IVT and neurological deterioration.

Patient Population

We retrospectively analyzed prospectively collected data for all acute stroke patients treated with IVT in the Neurological Departments of the University Hospitals of Basel, Bern, and Zürich; the Neurological Departments of the District Hospitals of Aarau, Münsterlingen, and St Gallen; and the Departments of Internal Medicine of the District Hospitals of Triemli and Waid between January 2001 and November 2004. These hospitals have a catchment area of ~3 500 000 inhabitants and are the only centers in the German-speaking part of Switzerland that offer IVT.

IVT Protocol

Each hospital involved in this study used its own institutional protocol for tPA administration. Patients were evaluated further only if they fulfilled the criteria applied by the NINDS study.3 All patients treated with IVT were admitted to intermediate- or intensive-care units, where they remained for at least 24 hours. An emergency CCT scan was performed after neurological deterioration.

Statistical Analysis

Normally distributed data were expressed as mean±SD and nonnormally distributed data as median and 95% confidence intervals (CIs).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

A total of 372 patients were treated with IVT during the observation period; 31 of them were excluded for not meeting the NINDS criteria (time window >3 hours); no ERISs and 1 SICH (3.2%) were diagnosed in these patients. Thus, 341 (92%) patients were further evaluated (Aarau, n=52; Basel, n=89; Bern, n=7; Münsterlingen, n=17; St Gallen, n=52; Triemli, n=24; Zürich, n=94; and Waid, n=6). There were 212 men and 129 women, aged 66±15 years (range, 16 to 94 years). NIHSS score on admission was 13 (median; 95% CI, 12 to 14; range, 2 to 25). Latency between symptom onset and initiation of treatment was 153±29 minutes (range, 10 to 180 minutes).

Recurrent Ischemic Stroke

ERIS was diagnosed in 2 (0.59%; 95% CI, 0.07% to 2.10%) patients. The first was a 72-year-old man with a history of diabetes mellitus and arterial hypertension who was admitted with a dense right hemiparesis, hemihypesthesia, dysarthria,
and fixed eye deviation to the left (NIHSS score, 16). Findings from the ECG and baseline CCT were normal. IVT was initiated 170 minutes after symptom onset. Forty minutes later, his level of consciousness rapidly decreased, and the patient became comatose. IVT was discontinued, and CCT performed immediately after neurological deterioration was still unremarkable. The third CCT performed 21 hours after the onset of initial symptoms showed multiple ischemic lesions in the territories of the left middle (with hemorrhagic transformation), anterior cerebral, and anterior choroidal arteries with compression of the left lateral ventricle and temporal horn; a midline shift and trans-tentorial herniation leading to displacement of the pons to the right side and compression of the fourth ventricle; ischemic lesions in the right middle cerebral artery (MCA); and probable ischemic lesions in the medial branch of the right posterior inferior cerebellar artery (Figure). Lesions in the territory of the right MCA and right posterior inferior cerebellar artery were not compatible with the initial symptoms. The patient died 3 days after symptom onset. Necropsy was not permitted.

The second patient was a 78-year-old woman admitted with dysarthria, left-sided weakness, hemihypesthesia, and hemianopia (NIHSS score, 11). The past medical history was unremarkable except for arterial hypertension. The ECG showed no ischemic changes but revealed a first-degree atrioventricular block; mediastinal widening was diagnosed on chest radiography. After normal CCT findings were observed, IVT was initiated 175 minutes after symptom onset. Fifty minutes after IVT initiation, the patient became comatose and developed generalized tonic seizures. IVT was discontinued. Findings on the emergency CCT were normal. CCT performed 6 hours after onset of the presenting stroke revealed an ischemic lesion in the territory of the right MCA and early demarcation of a further ischemic lesion in the territory of the left MCA. Bilateral occlusion of the internal carotid arteries was diagnosed on CCT angiography; this was presumed to be acute, as homogeneous, fresh, mainly hypo-echogenic thrombus was visualized in the lumen of both internal carotid arteries on extracranial color duplex sonography. The patient’s presenting symptoms were compatible with the diagnosed ischemic lesion in the territory of the right MCA but not with the second contralateral ischemic lesion. Abdomen and chest CT scans did not confirm the suspected aortic dissection but showed multiple, bilateral, acute kidney infarcts. The patient died on the third day after symptom onset. Necropsy was not permitted.

### Symptomatic Intracranial Hemorrhage
SICH occurred in 15 (4.40%; 95% CI, 2.48% to 7.15%) patients (8 of 190 [4.21%] patients treated at the university hospitals and 7 of 151 [4.64%] patients treated in community hospitals). Clinical details of the patients with SICH, the prevalence of vascular risk factors, pretreatment medications, relevant laboratory parameters, and latency between symptom onset and IVT and between IVT and subsequent neurological deterioration are displayed in the Table. None of these patients was treated with anticoagulants, unfractionated or low-molecular-weight heparin, or heparinoids on admission.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICH</th>
<th>ERIS</th>
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<tbody>
<tr>
<td>Age, y*</td>
<td>72 (66–77); range, 42–82</td>
<td>72, 78</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>NIHSS on admission*</td>
<td>13 (9–17); range, 5–22</td>
<td>16, 11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (40%)</td>
<td>2</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>8 (53.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>8 (53.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6 (40%)</td>
<td>1</td>
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<tr>
<td>100 mg</td>
<td>5</td>
<td>1</td>
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<tr>
<td>500 mg</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>159 (144–151); range, 100–193</td>
<td>140, 205</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>90 (80–100); range, 65–130</td>
<td>80, 130</td>
</tr>
<tr>
<td>Blood glucose, mmol/L*</td>
<td>7.1 (5.8–11.2); range, 4.6–17.8</td>
<td>12.6, 5.7</td>
</tr>
<tr>
<td>C-reactive protein, mg/L*</td>
<td>2.7 (1.3–22.1); range, 0.5–50</td>
<td>49, 19.8</td>
</tr>
<tr>
<td>Platelet count, 10^9/μL*</td>
<td>229 (208–271); range, 124–380</td>
<td>123, 244</td>
</tr>
<tr>
<td>Latency, onset to IVT, min*</td>
<td>155 (145–165); range, 130–180</td>
<td>170, 175</td>
</tr>
<tr>
<td>Latency, IVT to neurological deterioration, h*</td>
<td>12 (8–16); range, 2–22</td>
<td>...</td>
</tr>
</tbody>
</table>

*Values given are median (95% CI) and range.†Values given are arterial blood pressure values on admission. All patients with blood pressure values >180 mm Hg (systolic) or 100 mm Hg (diastolic) were treated with antihypertensives (mainly nitrates) before IVT initiation.
The international normalized ratio ranged between 0.9 and 1.1, and activated partial thromboplastin time was within the normal range in all cases. Hematomas were located in the infarcted area in 13 patients (space-occupying effect in 5 patients; intraventricular extension in 1 patient). A right pontine hemorrhage occurred in 1 and a left occipital hemorrhage in another patient; initial ischemic lesions were located in the territory of the right MCA in both cases.

**Discussion**

The present study is the first report of ERIS in patients with acute ischemic stroke treated with IVT; furthermore, the size of the present study and the fact that it presents population-based data from patients receiving tPA under a predefined protocol allow valid conclusions concerning its incidence. Although recurrent ischemic stroke was assessed in the NINDS trial, the time point of neurological deterioration was not specified, and the pathophysiological mechanism proposed in the present study was not postulated.

The diagnosis of ischemic lesions in multiple cerebral vascular territories in 1 patient and in both MCA territories and both kidneys in the second patient are highly suggestive of the disintegration and subsequent scattering of cardiac or aortic thrombi as the underlying etiology of ERIS. Obviously, disintegration of thrombi can occur spontaneously and is not necessarily associated with tPA administration. Still, the fact that neurological deterioration occurred 40 to 50 minutes after tPA initiation in both cases strongly argues for a causative role of tPA. The only possible means for resolving this issue would be a randomized study comparing the incidence of ERIS between stroke patients treated with IVT and controls; still, such a study would not be ethical, taking into account that IVT constitutes a treatment of proven efficacy for patients with acute ischemic stroke. A registry of patients with ERIS after IVT could provide more information on this intriguing issue.

Unfortunately, no necropsy was performed in the 2 patients; the same was true for echocardiography, which was withheld owing to the lack of therapeutic consequences. We can thus provide no evidence of underlying cardiac or aortic disease to support our hypothesis. Considering that the cause of ERIS both from the clinical and the imaging viewpoint was clearly embolic, it is questionable whether this information would be of great assistance, the basic unanswered question being the causative role of tPA rather than the source of embolic material.

Previous coronary thrombolysis trials reported a 0.4% to 0.7% incidence of ischemic stroke until hospital discharge or for the following 30 to 35 days. Only 1 study described the incidence of ischemic stroke within the first 6 hours after thrombolysis, which was 0.13%. Comparison of these results with those of the present study is inconclusive, owing to differences in treatment protocols with regard to the dose and duration of tPA infusion and the concomitant use of aspirin, heparin, or both. Furthermore, CCT scans were not always part of the diagnostic work-up for presumed stroke in coronary trials, rendering the determination of true ischemic stroke prevalence impossible.

Obviously, the incidence of ERIS is far too low to justify delay of IVT initiation, considering the demonstrated higher benefit associated with earlier IVT treatment. Furthermore, transesophageal echocardiography, the sole method capable of excluding the possibility of intracardiac or aortic thrombi, can barely be performed within the 3-hour window and is not available on a 24-hour basis. We must point out, however, that the true incidence of ERIS was potentially underestimated in this study, because we evaluated only those patients with a deterioration ≥4 points on the NIHSS.

Although the differences in temporal occurrence of ERIS and SICH are intriguing, they obviously do not allow a definite distinction between these 2 entities in an individual patient. Thus, neurological deterioration should prompt discontinuation of IVT and performance of an urgent CCT scan. Our findings should alert treating physicians to the possibility that deterioration during IVT is not necessarily due to ICH but can also be caused by ERIS. We propose that patients with ERIS should undergo urgent diffusion- and perfusion-weighted MRI to estimate the extent of both the ischemic lesions and the associated pENUMbra. The results of these MRI studies will be helpful to guide patient management, in particular, to resolve the question of whether further therapeutic regimes such as local intra-arterial or mechanical thrombolysis should be taken into consideration. Exclusion of SICH in these cases should be by no means prompt a wait-and-see attitude.

**Disclosures**

None.

**References**


The present study provides the first description of early recurrent ischemic stroke (ERIS) as the cause of neurological deterioration in acute stroke patients who are undergoing intravenous thrombolysis. Prospectively collected, population-based data for 341 consecutive acute stroke patients treated with tissue-type plasminogen activator (tPA) at 8 medical centers in Switzerland were retrospectively analyzed. ERIS was defined as neurological deterioration ≥ 4 points on the National Institutes of Health Stroke Scale that occurred within 24 hours of tPA treatment, suggesting the involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on cranial computed tomography scans, in the absence of intracranial hemorrhage (ICH). The incidence of this complication was low, as it occurred in only 2 of 341 patients (prevalence, 0.59%; 95% confidence interval, 0.07% to 2.10%). The diagnosis of multiple ischemic lesions in both patients suggests the disintegration and subsequent scattering of cardiac or aortic thrombi as the underlying etiology. Furthermore, we observed a different temporal pattern compared with that for ICH, with both ERISs occurring during thrombolysis and all 15 symptomatic ICHs occurring 2 to 22 hours after termination of tPA infusion. These findings should alert treating physicians to the possibility that deterioration during intravenous thrombolysis is not necessarily due to ICH but can also be caused by ERIS. Exclusion of ICH in these cases should by no means prompt a wait-and-see attitude but rather should lead to urgent magnetic resonance imaging studies and, potentially, additional therapeutic interventions such as local thrombolysis.
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