Good Outcomes in Ischemic Stroke Patients Treated With Intravenous Thrombolysis Despite Regressing Neurological Symptoms

Christian R. Baumann, MD; Ralf W. Baumgartner, MD; Joubin Gandjour, MD; Hans-Christian von Büdingen, MD; Adrian M. Siegel, MD; Dimitrios Georgiadis, MD

**Background and Purpose**—We evaluated the clinical course of 19 acute stroke patients with rapid early improvement of neurological deficit within the 3-hour window, treated with intravenous thrombolysis.

**Results**—No patient demonstrated a neurological deterioration during hospitalization. National Institutes of Health Stroke Scale (NIHSS) scores at therapy decision and discharge were 5 (4 to 6) and 0.5 (0 to 1.5), respectively. At 3-month follow-up, 1 patient had died; in remaining patients, NIHSS was 0 (0 to 1) and modified Rankin Scale 0.5 (0 to 1; ≤1 in 15 patients).

**Conclusions**—Withholding of intravenous thrombolysis because of spontaneous early regression of neurological symptoms may not be justified. (Stroke. 2006;37:000-000.)

Key Words: cerebrovascular disorder ■ thrombolysis

On weighing the theoretically small potential benefit against the risk of intracranial hemorrhage, many stroke physicians are reluctant to perform intravenous thrombolysis (IVT) in acute stroke patients with rapid early improvement (REI) of neurological deficit. This is in accordance with the current guidelines for the early management of acute stroke, recently published in this journal. It must be noted, though, that no data on this issue can be derived from published thrombolysis trials, because minor or rapidly improving stroke symptoms constituted an exclusion criterion. Mounting evidence on the other hand suggests that REI carries a significant risk of subsequent neurological deterioration at a time-point precluding thrombolytic treatment.

**Patients and Methods**

The Zurich Thrombolysis Registry was set up in July 1997 to prospectively collect data from all acute stroke patients treated with IVT in our institution. IVT was performed according to the National Institute of Neurological Disorders and Stroke rt-PA Stroke (NINDS) study criteria. All patients treated with IVT were admitted to intermediate or intensive care units, where they remained for at least 24 hours under continuous medical surveillance. As from October 2002, after the publication of the first study describing a grave prognosis in one third of acute stroke patients not treated with IVT attributable to REI or mild symptoms, this protocol was modified to allow IVT application in patients with REI. Data from all patients treated with IVT between October 2002 and August 2005 was retrospectively analyzed for the purposes of this study, which was performed according to local ethical committee standards.

REI was defined as regression of neurological symptoms between stroke onset and evaluation by the treating neurologist. As the initial evaluation of most patients was performed at the place of symptom onset by an emergency physician, who was not necessarily a neurologist, National Institute of Health Stroke Scale (NIHSS) score was rarely assessed. We therefore defined the following items, which could reliably be calculated on retrospective motor paresis of (1) arm, (2) leg or (3) facial muscles; (4) aphasia, (5) dysarthria and (6) sensory deficit. Only patients with a documented significant improvement in at least 4 items were further evaluated in this study. Significant improvement was defined as regression of (a) severe or total motor paresis to mild paresis or normal power, (b) muteness or inability to communicate to mild aphasia (difficulty in finding isolated words, fluent paraphasic speech or reduced speech production, nevertheless allowing an adequate communication), (c) inability to articulate to slight articulation problems and (d) any sensory deficit to no sensory deficit. Thus, the theoretical range of the neurological improvement varied between 4 and 22 points of the NIHSS.

Neuroradiological examinations entailed cranial CT, performed on admission, 24 hours after IVT completion and 3 to 5 days after symptom onset in all patients; additionally, MRI was performed 3 to 5 days after symptom onset in 15 patients. Diagnostic work-up consisted of ultrasound examinations of the brain-supplying arteries, 12-lead ECG, and—in selected patients—24-hour Holter (n=14) and transesophageal echocardiography (n=12). Stroke etiology was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Functional outcome was assessed using the NIHSS and modified Rankin Scale (mRS). Follow-up examinations were performed in every patient at dismissal, and at 3 months (107±23 days) in our outpatient department. Good outcome was defined as mRS 0 or 1. Neurological deterioration was defined as any deterioration measurable on the NIHSS.

**Results**

Inclusion criteria were met in 19 (12%) of 158 patients (4 women, 15 men; mean age 59±13 years, range 19 to 78...
years) treated with IVT during the surveillance period. NIHSS at therapy decision was 5 (4 to 6; median [95% CI]; range 1 to 6).

Cranial CT on admission was normal in 10 patients; early signs of ischemic stroke were seen in 6 and dense middle cerebral artery sign in 3 patients. Latency between symptom onset and IVT initiation was 154±30 minutes (range 102 to 180 minutes). Etiology of stroke was cardioembolic in 8 (42%), large artery atherosclerosis in 4 (21%), other determined etiology in 2 (11%; internal carotid artery dissection in both cases) and undetermined in 5 (26%) patients. Seven patients were receiving antiplatelet agents before stroke.

No patient demonstrated a neurological deterioration during hospitalization. Lacunar infarcts were diagnosed in 4 patients; in remaining patients, infarct size was <1/3 (n=11) or >1/3 but ≤2/3 of the middle cerebral artery territory (n=4). Asymptomatic hemorrhagic transformation of the ischemic lesion without space-occupying effect was observed in 4 (21%) patients. No parenchymal hemorrhages were diagnosed. NIHSS score at discharge was 0.5 (0 to 1.5; median and 95% CI). Antiplatelet agents were administered in 12, warfarin in 7, and statins in 13 patients.

During 3-month follow-up, 1 patient with intermittent atrial fibrillation and insufficient oral anticoagulation died from recurrent ischemic strokes. In all other patients, symptoms improved or at least remained stable, without signs of recurrent ischemic or hemorrhagic stroke. NIHSS at 3 months in remaining patients was 0 (0 to 1) and mRS 0.5 (0 to 1; median [95% CI]; ≤1 in 15 and 2 in 3 patients).

Discussion
Existing data concerning the prevalence of REI within the first 3 hours after symptom onset in patients with acute ischemic stroke and the natural history of these patients is limited: O’Connor et al and Cocho et al observed resolution of deficit in 31/214 (14.5%) and 11/218 (5%) patients, respectively, but provided no data on their clinical course. Barber et al described resolution of symptoms in 57/314 (18.2%) patients; only 1 of the 21 patients documented to have had a major motor improvement was discharged from hospital independent, whereas 32% of patients not treated with IVT attributable to mild or significantly improving neurological symptoms were either dependent at discharge or dead during hospital admission. Smith et al reported mild neurological deficit or REI (defined as NIHSS improvement ≥4 points) as the most common reason for exclusion from IVT (41 of 71 patients; 58%). The prevalence of REI was 7.8% (10/128 patients). Four of these patients could not be discharged home; 2 died. REI was identified as the only clinical feature associated with subsequent neurological worsening. These results suggest that the issue of REI is relevant, as it concerns a significant (5% to 18%) portion of acute stroke patients eligible for IVT, and is associated with severe subsequent deterioration in approximately one third of patients.

No neurological worsening was observed in any of our 19 patients. The remarkably good outcome observed in this study was probably attributable to the fact that neurological deficit before IVT initiation was quite low (median NIHSS score of 5). Obviously, the present study was not randomized and the patient count is low; additionally, some REI cases were potentially missed because of the rigorous definition applied. Still, comparison of the course of our patients to the natural course described above suggests that IVT should not necessarily be withheld solely because of regressing neurological symptoms. This issue should be addressed in a randomized clinical trial, as it concerns a substantial number of acute stroke patients, who could potentially benefit from thrombolytic treatment.

References
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*Stroke*. published online March 23, 2006;

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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