Thrombolysis Beyond the Guidelines

Two Treatments in One Subject Within 90 Hours Based on a Modified Magnetic Resonance Imaging Brain Clock Concept

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Background and Purpose—We report the first case of 2 intravenous thrombolysis treatments within 90 hours in a patient with early recurrent stroke.

Summary of Review—A 50-year-old man had improved significantly after intravenous thrombolysis for acute stroke. On the fourth day, he deteriorated dramatically because of recurrent stroke. Evidence of vessel reocclusion and profound perfusion/diffusion mismatch constituted the rationale for a second thrombolysis treatment, which resulted in vessel recanalization and significant neurologic improvement.

Conclusion—The pathophysiological information obtained by multimodal magnetic resonance imaging may suit as a brain clock when repeat thrombolysis treatment is considered for early recurrent stroke. (Stroke. 2005;36:e162-e164.)

Key Words: magnetic resonance imaging ■ stroke ■ thrombolysis

A 50-year-old man was admitted because of sudden onset of left-sided hemiparesis and slurred speech. Neurologic examination revealed some effort against gravity in his left arm and a drift of his left leg. There was sensory loss in the paretic limbs. He had a partial gaze palsy to the left, near total paralysis of his left lower face, and mild dysarthria. National Institute of Health Stroke Scale (NIHSS) score was 9. He was not taking any regular medication and denied any relevant preexisting disease.

Magnetic resonance imaging (MRI) was performed on a 1.5-T unit (Magnetom Symphony; Siemens) with a standard head coil. The imaging protocol included diffusion-weighted spin-echo echo planar imaging (DWI), fluid-attenuated inversion recovery (FLAIR), 3D-time-of-flight (TOF)-MR angiography (MRA), and dynamic susceptibility contrast perfusion imaging using a gradient-echo echo planar imaging sequence. For perfusion MRI, Gadovist (Schering) was applied with a dosage of 0.2 mL/kg body weight through an automated injector (Ohio Tandem; Ulrich) at a flow rate of 5 mL/s. All sequences were applied in transverse orientation; total imaging time was <8 minutes. Color-coded maps of relative mean transit time (rMTT) were calculated on a separate workstation (Perfusion MR card Leonardo, software version VD10B; Siemens) using a commercially available software according to the method described by Ostergaard.1 The region of interest for the arterial input function was defined manually near the middle cerebral artery (MCA) of the normal hemisphere. The postprocessing was performed immediately after data acquisition available at the time the clinical decisions were made.

MRI showed diffusion restriction in the right basal ganglia, internal capsule, and corona radiata. There was an obvious mismatch of DWI and perfusion images with perfusion deficit concerning most of the right MCA territory. TOF-MRA showed occlusion of the right distal M1 segment (Figure 1A through 1D).

After informed consent, intravenous thrombolysis (IVT) with 90 mg recombinant tissue plasminogen activator (rtPA) was started exactly 2 hours after stroke onset, the dosage of rtPA after the SITS-MOST protocol (0.9 mg/kg, maximum 90 mg).2 After 24 hours, there was significant improvement of motor function (NIHSS score: 6), whereas MRI showed infarction in the areas of diffusion restriction found in the initial examination and additionally in the insula. TOF-MRA demonstrated vessel recanalization (Figure 1E through 1G).

Duplex ultrasound revealed occlusion of the left internal carotid artery (ICA) and 80% stenosis of the right ICA with predominantly echolucent plaques. Endarterectomy of the right ICA was planned to be performed soon. He received 75 mg/d clopidogrel, 5 mg/d lisinopril, 10 mg/d simvastatin, and early rehabilitation. On the third day, motor function was nearly normal. The sensory deficits had improved, and dysarthria was not detectable.

On the fourth day, he suddenly deteriorated dramatically without any significant change in blood pressure. He was not able to raise his left arm, and there was marked dysarthria and worsening of the facial palsy and sensory deficits. NIHSS...
The score was 10. MRI demonstrated the previous infarction in an identical configuration on DWI and FLAIR images. However, again, there was a significant perfusion/diffusion mismatch with a large perfusion deficit, especially in the anterior territory of the right MCA. TOF-MRA showed occlusion of a right M2 segment (Figure 2A through 2D). Considering the dramatic deterioration and the imaging findings, we discussed the management options with the patient. It was pointed out that a second IVT within 90 hours after the first treatment is...
contraindicated as long as we follow our protocol and the summary of product characteristics of Actilyse (Boehringer Ingelheim Pharma KG). There, any prior stroke within the last 3 months is listed as a contraindication for IVT. The patient was told that for a second IVT treatment, the risk of intracranial hemorrhagic complications was expected to be considerably higher. Despite potential risks, the patient was convinced that IVT would again be beneficial. We decided to give a reduced dose of rtPA, ie, 50 mg (10% as bolus, rest of infusion in 1 hour). Treatment started 85 minutes after the sudden deterioration with informed consent. Twenty-four hours later, TOF-MRA showed vessel recanalization. Perfusion imaging had normalized, and there were no additional infarcts on DWI and FLAIR images (Figure 2E through 2H). Forty-eight hours later, the NIHSS score was 6.

Four days after the second stroke, endarterectomy of the right ICA was performed successfully. He made good rehabilitation progress. Three months later, his neurologic deficits were a mild facial palsy and restriction of fine movements of the left hand (modified Rankin Scale score: 1).

**Discussion**

To the best of our knowledge, this is the first report on a patient who received 2 treatments with intravenous rt-PA for acute ischemic stroke within 90 hours.

The management of patients with early recurrent stroke is one of the most challenging issues of modern stroke care. In this clinical setting, guidelines are of limited help. In particular, the role of specific recanalization strategies is not clear. Use of rtPA in this situation is off-label. However, is a second treatment with rtPA within several days hazardous? rtPA is cleared rapidly from the circulating blood and metabolized mainly by the liver. The plasma half-life $t_{1/2}$ alpha is 4 to 5 minutes, and the beta-half-life is approximately 40 minutes. A marked and prolonged decrease of the circulating fibrino-
gen level is unusual. Repeat IVT within a short interval may involve a considerable risk of serious hemorrhage, especially in previously infarcted areas. In our patient, the infarcted area in the 24-hour FLAIR images after the first treatment was rather small. With respect to the presumed higher bleeding risk in case of another full dose of rtPA, the second IVT was carried out with a reduced dose. After the dramatic deterioration, evidence of vessel recoclusion and the significant perfusion/diffusion mismatch indicating the tissue at risk constituted the rationale for a second IVT. The pathophysiological information obtained by the mismatch may be viewed as a brain clock replacing the epidemiologic time clock when IVT is considered. However, the perfusion/diffusion mismatch is an unproven hypothesis yet. Ongoing trials have to confirm this concept. In our patient, we modified this theoretical brain clock concept, using it not for thrombolysis beyond the 3-hour time window, but for a second treatment within 90 hours. We are aware of the fact that the safe implementation of IVT in clinical routine has just begun. For safety reasons, inexperienced centers are well advised to follow the recommendations of current guidelines. In centers with years of experience in stroke management and thrombolysis, multimodal MRI can provide useful information that may justify individualized clinical decisions.

**References**

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