Utility of Early Post-treatment Single-Photon Emission Computed Tomography Imaging to Predict Outcome in Stroke Patients Treated with Intravenous Tissue Plasminogen Activator

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It is important to predict the outcome of tissue plasminogen activator (tPA)–treated patients early after the treatment for considering the post-tPA treatment option. We assessed cerebral blood flow (CBF) of tPA-treated patients with single-photon emission computed tomography (SPECT) 1 hour after tPA infusion to predict the patient outcome. Technetium-99m-hexamethylpropyleneamine oxime SPECT was performed in 35 consecutive tPA-treated patients. Asymmetry index, a contralateral-to-ipsilateral ratio of CBF, was calculated to analyze CBF quantitatively. Hypoperfusion or hyperperfusion was defined as a decrease of 25% or more or a increase of 25% or more in asymmetry index, respectively. Of all 35 patients, 23 had only hypoperfusion, 8 had both hypoperfusion and hyperperfusion, 2 had only hyperperfusion, and 2 had no perfusion abnormality. When evaluating the association between hypoperfusion and outcome, hypoperfusion volumes were significantly correlated with the modified Rankin Scale at 3 months ($r = .634$, $P < .001$). Hyperperfusion was observed in 10 patients (28.6%) and they showed a marked National Institutes of Health Stroke Scale score improvement in the first 24-hour period, which were significantly greater than those of 25 patients without hyperperfusion ($P = .033$). Eight patients (22.9%) with intracerebral hemorrhage (ICH) were all asymptomatic. Most ICHs were located in hypoperfusion areas, and no ICH was related to hyperperfusion. The results of the present study demonstrated that hypoperfusion volume was associated with poor outcome, whereas the presence of hyperperfusion seemed to be predictive of symptom improvement but not of development of ICH. Taken together, early post-treatment SPECT imaging seems to be a useful biomarker of outcome in tPA-treated patients. **Key Words:** Acute ischemic stroke—tPA—SPECT—hypoperfusion—hyperperfusion.

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Intravenous tissue plasminogen activator (tPA) therapy has been established as a standard first-line treatment for acute ischemic stroke. The accumulation of cases with intravenous tPA therapy has shown the benefits and limitations of this therapy. Postmarketing studies showed that the percentage of good outcomes (modified Rankin scale [mRS] score 0-1) varied from 32% to 39%, whereas those of poor outcomes (mRS score 4-6) varied from 20% to 47%.[1] The percentage of poor outcomes is not low and still

needs to be reduced. Therefore, it is important to predict the outcome of tPA-treated patients early after the treatment for considering the post-tPA treatment option.

Because brain ischemic damage is associated with the severity and duration of ischemia, therapeutic outcome of intravenous tPA therapy depends on the degree and timing of revascularization, divided into recanalization and reperfusion, in ischemic brain tissue. Recanalization after tPA therapy was noted in around 50% of patients with middle cerebral artery occlusion at 6 hours after stroke onset.[2,3] Although recanalization of the occluded artery is critical in acute ischemic stroke, recanalization does not always mean appropriate reperfusion or restoration of blood flow in the vascular bed.[4] No-reflow phenomenon has been well documented in animal transient ischemic models.[5-7] Meanwhile, hyperperfusion demonstrated in the clinical radiological examination is known as another abnormal reperfusion pattern after recanalarization[8]; however, it is uncertain to what extent and how often reperfusion abnormality happens in the clinical course of tPA-treated patients; therefore, it is important to evaluate cerebral perfusion after intravenous tPA therapy to predict the therapeutic outcome. Another concern after intravenous tPA therapy is the risk of developing hemorrhagic transformation, which is the main issue in therapeutic safety. Symptomatic intracerebral hemorrhage (ICH) is the most difficult complication to deal with during thrombolytic and antithrombotic therapy and is associated with a poor outcome; therefore, it is important to predict the development of ICH on tPA therapy.

Based on this background, we attempted to measure the cerebral blood flow (CBF) of tPA-treated patients to predict outcome in the early post-treatment period by using single-photon emission computed tomography (SPECT) with technetium-99m-hexamethylpropyleneamine oxime (^{99m}TcHMPAO). We analyzed the association of cerebral perfusion and the therapeutic outcome including the development of hemorrhagic transformation after intravenous tPA therapy.

Methods

Subjects

This is a retrospective analysis of prospectively collected data in 35 consecutive tPA-treated patients because of ischemic stroke in the anterior circulation. A total dose of .6 mg/kg tPA with 10% of the dose given as a bolus was administrated for 60 minutes within 3 hours of the initial symptoms following the directions for use of tPA in Japan. The severity of the patients' neurologic deficits was assessed before and after t-PA therapy with the National Institutes of Health Stroke Scale (NIHSS; scored from 0 to 31). Clinical outcome was measured at 3 months with mRS.

Magnetic Resonance Imaging and Computed Tomography Scans

An emergent magnetic resonance imaging (MRI) scan was performed with 1.5 T MRI systems before tPA therapy in all stroke patients without contraindications to MRI. The emergency MRI protocol consisted of diffusion-weighted imaging (DWI), fluid attenuation inversion recovery image, T2-weighted imaging, and MR angiography. Follow-up MRI scans were performed at days 2 and 7. When hemorrhagic transformation was suspected by MRI scans, a CT scan was added to confirm the hemorrhagic findings.

SPECT Imaging

^{99m}Tc-HMPAO SPECT was performed 1 hour after tPA therapy using a double-head rotating γ-camera (ECAM; Toshiba, Tokyo, Japan) equipped with a fan beam collimator. After intravenous injection of 740MBq of ^{99m}Tc-HMPAO, dynamic planar images were obtained immediately for 2 minutes, and then the collection of SPECT data was started at 5 minutes after the injection with the following parameters: 64 × 64 matrix, 180° rotation, and 45 views per detector and 4 times of acquisition repeated (total imaging time, 20 minutes). Patlak plot method developed by Matsuda et al[9] was employed to convert from SPECT images to CBF images. This method depends on graphic analysis to evaluate the unidirectional influx constant of the tracer form the blood to the brain.[9] The acquired individual CBF data were anatomically normalized to the standard brain by NEUROSAT developed by Minoshima et al.[10] This method involves linear scaling to correct an individual brain size and nonlinear warping to minimize regional anatomic variation among subjects, resulting in facilitating pixel-by-pixel comparisons of CBF images.[10] To perform semi-quantitative analysis of CBF, asymmetry index, a contralateral-to-ipsilateral ratio of CBF, of each symmetrical pixel was obtained with the following equation: $[1 - (CBF_{ipsi}/CBF_{contra})] \times 100\%$. Hypoperfusion was defined as a CBF decrease of 25% or more compared with the contralateral CBF using the asymmetry index. The reason why the 25% threshold was chosen for the definition of hypoperfusion was that the 25% threshold provided a more similarity between hypoperfusion areas in asymmetry index image and DWI lesion areas compared with 20% or 30% threshold (Fig 1). Meanwhile hyperperfusion was defined as a CBF increase of 25% or more compared with the contralateral CBF to match the threshold magnitude of hypoperfusion. To quantitatively analyze the hypoperfusion volume, it was quantified as the percentage of the ipsilateral hemispheric volume. We assessed the association of cerebral perfusion and the patient outcome including the development of hemorrhagic transformation after intravenous tPA therapy.