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Diagnostic impact of baseline cerebral blood flow in patients with acute ischemic stroke prior to intravenous recombinant tissue plasminogen activator therapy

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ABSTRACT

Objective: To determine whether severe cerebral perfusion defects measured by SPECT prior to rt-PA therapy attribute to severe intracerebral hemorrhage (SICH).
Methods: We measured baseline cerebral blood flow (CBF) using technetium-99m-labeled hexamethylpropyleneamine oxime (99mTc-HMPAO) SPECT qualitatively prior to rt-PA therapy, in 52 consecutive patients (range 38–93 years). The degree and extent of the asymmetry of local CBF were analyzed semiquantitatively. We did not administrate rt-PA in patients with severe perfusion defects. Clinical outcome and the incidence of SICH were studied.
Results: Three (5.8%) patients had severe perfusion defects that were undetected by CT and/or DWI. The other 49 (94.2%) patients had mild perfusion defects. The asymmetry of local CBF was 0.08 ± 0.08 ($n = 3$) and 0.3 ± 0.15 ($n = 49$) in the two groups, respectively. The percentages of the ipsilateral hemisphere in which perfusion was impaired severely were $17.5 \pm 9.5\%$ ($n = 3$) and $0.43 \pm 0.87\%$ ($n = 49$). Two patients were found petechial hemorrhage, but there was no patient who developed SICH in the former group following conventional antithrombotic therapy. In the latter group, SICH occurred in 1/49 (2.0%) patient following rt-PA therapy.
Conclusion: These results suggest that rt-PA therapy for patients with severe cerebral perfusion defects may cause SICH and baseline CBF may contribute to identify patients at high risk for SICH after intravenous rt-PA therapy.

1. Introduction

Despite an increased risk of severe hemorrhagic transformation (HT), intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has been demonstrated to improve outcome in patients when administered within the first 3 h after the onset of acute ischemic stroke symptoms [1]. Rapid treatment is associated with better outcomes at 3 months, as demonstrated by pooled analysis of 6 randomized placebo-controlled trials of intravenous rt-PA [2]. The odds of a favorable 3-month outcome increased as the onset-to-treatment time decreased. The urgency of this therapy, therefore, precludes extensive neuroimaging studies. Indeed, there was no requirement to demonstrate vascular and perfusion status prior to treatment in the National Institute of Neurological Disorders (NINDS) rt-PA Stroke Study or in the guidelines for intravenous rt-PA usage published by the Japan Stroke Society [1,3]. However, the occurrence of severe intracerebral hemorrhage was shown to be associated with rt-PA treatment and age, but not with onset-to-treatment time or baseline neurological severity [2]. Knowledge of risk factors for severe HT may improve the selection of patients and the safety of treatment. As discussed by Larrue et al., interpretation of the risk factors for HT is difficult because of the inconsistent classification of HT [4]. However, the presence of early ischemic changes on pretreatment CT scans has been confirmed as a risk factor for severe HT [4–8]. Diffusion-weighted magnetic resonance imaging (DWI) findings obtained before rt-PA thrombolysis have been shown to predict stroke outcome using the Alberta Stroke Programme Early CT Score (ASPECTS), a well-known standardized quantitative CT grading system for patients with early stroke [9]. Using such analysis, neurological improvement was seen in only 25% of patients with a poor DWI-ASPECTS score, while 75% had a bad outcome even if early recanalization after rt-PA infusion occurred. In other words, patients with severe ischemic damage may not only have a low chance of clinical

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Table 1
Demographic data.

	Mild hypoperfusion group ($n=49$)	Severe hypoperfusion group ($n=3$)
Age (years)	74 ± 12	74 ± 14
Male	24 (50%)	2 (67%)
Baseline NIHSS	15 ± 6.1	20 ± 1.7
Occluded artery		
ICA	10	3
M1	14	0
M2	9	0
BA	0	0
Time from onset to treatment (min)	125 ± 24	93 ± 2.9

NIHSS, National Institutes for Health Stroke Scale; ICA, internal carotid artery; M1, middle cerebral artery M1 segment; M2, middle cerebral artery M2 segment; BA, basilar artery.

recovery after treatment with rt-PA thrombolysis, but may also be further harmed by thrombolytic treatment. Therefore, determination of cerebral perfusion status prior to rt-PA therapy would be ideal as long as time allows. Very recently, Souza et al. denoted that CT perfusion (CTP)-based hypoperfused tissue volume and thresholded mean voxel values were markers of HT in acute stroke, with similar accuracy to DWI [10]. However, they also denoted that perfusion status maps based on CTP likely failed to show a correlation with HT due to an insufficiently long acquisition time to accurately measure this parameter; many centers which perform CTP have similarly short acquisition times, especially given recent concerns regarding CTP radiation dose.

Therefore, we performed single-photon emission computed tomography (SPECT) for as many patients as possible to determine their cerebral perfusion status at baseline, to detect patients with deep and extensive cerebral ischemia, and to exclude patients at risk of severe HT from rt-PA therapy. We report the outcome and incidence of severe HT in 52 patients who underwent SPECT scans before rt-PA treatment and discuss the feasibility and effectiveness of using SPECT to determine the appropriate use of rt-PA therapy within 3 h of onset acute ischemic stroke.

2. Patients and methods

2.1. Selection of patients

Consecutive patients treated within 3 h of acute ischemic stroke onset were studied retrospectively between October 2005 and November 2009. Inclusion and exclusion criteria for intravenous rt-PA were in accordance with the guidelines published by the Japan Stroke Society [3]. All patients underwent CT and/or DWI scans before the treatment. Patients with signs of intracerebral hemorrhage or early ischemic change affecting >33% of the middle cerebral arterial territories, including parenchymal hypo-attenuation on CT, parenchymal hyperintensity on DWI, and brain swelling, were excluded from the present study. All subjects included in this study have received an injection of an isotope (technetium-99m-labeled hexamethylpropyleneamine oxime; 99mTc-HMPAO) for the SPECT scan and had technically adequate SPECT scans that were carried out within 3 h of symptom onset but before rt-PA administration. Finally, rt-PA therapy was contraindicated in patients who had a region of severe hypo- or no-perfusion on SPECT, even if extensive early ischemic change did not exist on CT and/or DWI (severe hypoperfusion group). Patients having only mild perfusion defects on SPECT (mild hypoperfusion group) underwent rt-PA therapy. Of the 121 patients who received rt-PA therapy during the study period, 52 were included. The demographic data are presented in Table 1.

2.2. SPECT methodology

All patients had a SPECT scan before treatment to qualitatively measure cerebral blood flow (CBF) using a dual-head variable-geometry nuclear imaging system (Millennium VG, GE Healthcare Japan, Tokyo, Japan). Patients were administered 99mTc-HMPAO intravenously at the nuclear medicine laboratory if no intracranial hemorrhage or early ischemic changes were revealed by CT and/or DWI. The total SPECT scanning time was approximately 15–20 min. The 99mTc-HMPAO SPECT images were used to visualize the affected hemisphere and identify low perfusion areas. To investigate the patients' perfusion status and determine the extent of the hypoperfusion, asymmetry of local CBF was semi-quantitatively analyzed using commercially available software, iSSP version 5 and Focus Viewer version 2.0 (Nihon Medi-Physics Co. Ltd., Tokyo, Japan). The ratio of local CBF in the ipsilateral to contralateral hemispheres was calculated on a pixel-by-pixel basis. In the present study, the local cerebral perfusion status was rated as severe hypo- or no-perfusion when the asymmetry of local CBF was less than 0.3. The percentage of the affected region was then calculated as the number of pixels in the affected region in which the asymmetry was less than 0.3 to that of the whole ipsilateral hemisphere, indicating both the depth and extent of the perfusion defect.

2.3. Outcome determination

The efficacy of intravenous rt-PA therapy was evaluated 3 months after treatment using the modified Rankin scale (mRS). The incidence of HT after treatment was also evaluated. As previously reported, HT was classified according to clinical and radiological criteria [4]. We counted the number of patients with the following conditions: (1) any intracranial hemorrhage occurring within 3 days of admission and (2) symptomatic intracerebral hemorrhage (SICH). SICH was defined as parenchymal hematoma type II with mass signs of parenchymal hematoma that worsened by at least 4 points on the National Institutes of Health Stroke Scale (NIHSS) [4,5,11].

All continuous variables were expressed as mean ± standard deviation.

3. Results

3.1. Asymmetry of regional CBF on 99mTc-HMPAO SPECT prior to rt-PA therapy

The study cohort comprised 161 consecutive patients with acute ischemic stroke admitted to our hospital within the first 3 h of onset during the aforementioned period. Of these patients, 40 were not eligible for rt-PA treatment, according to the guidelines for rt-PA usage in Japan. For 69 patients, there was insufficient time to undergo a SPECT scan within 3 h of stroke onset. Finally, 52 patients (26 males; mean age, 74.4 ± 11.6 years) were enrolled. The time from symptom onset to the start of treatment was 123 ± 23.1 min.

Qualitative inspection of the CT, DWI, and 99mTc-HMPAO SPECT images revealed a mismatch between the extent of decreased CBF and the extent of the hyper-intense signal area on DWI or hypo-attenuated area on CT in all 52 patients. Of these patients, 49 (94.2%) had a mild perfusion defect (mild hypoperfusion group) and the other 3 (5.8%) had a severe perfusion defect (severe hypoperfusion group) as revealed on SPECT. Asymmetry of local CBF was semi-quantitatively analyzed in these 52 patients retrospectively (see above). As a result, the worst ratio of local CBF in the ipsilateral hemisphere was 0.3 ± 0.15 ($n=49$) in the mild hypoperfusion and 0.08 ± 0.08 ($n=3$) in the severe hypoperfusion group.