Table 1. Clinical Characteristics and MRI Findings Before Tissue-Type Plasminogen Activator Infusion Between Patients With Complete Recanalization and Partial Recanalization

Clinical Symptoms, %	Complete Recanalization (N=16)	Partial Recanalization (N=33)	*P*
Female	5 (31.3%)	19 (57.6%)	0.0839
Age, y	74.4±7.9	77.3±11.4	0.2084
Hypertension	11 (68.8%)	20 (60.6%)	0.5792
Diabetes mellitus	2 (12.5%)	6 (18.2%)	0.6138
Hyperlipidemia	4 (25.0%)	3 (9.1%)	0.1359
Smoking	5 (31.3%)	10 (30.3%)	0.9462
Atrial fibrillation	8 (50.0%)	20 (60.6%)	0.4817
Stroke type			
Cardioembolic stroke	10 (62.5%)	19 (57.6%)	0.7422
Large artery disease	0 (0.0%)	1 (3.0%)	0.9999
Use of antiplatelet therapy			
Warfarin	1 (6.3%)	2 (6.1%)	0.9999
Aspirin	4 (25.0%)	9 (27.3%)	0.9999
National Institutes of Health Stroke Scale score	14.8±6.0	15.4±6.6	0.6933
Systolic blood pressure, mm Hg	144.4±24.2	153.9±18.5	0.1563
Diastolic blood pressure, mm Hg	81.1±16.0	81.3±16.3	0.9067
Time from symptom onset to treatment, min	139.1±37.0	132.3±29.6	0.2769
Time from end of tissue plasminogen activator infusion to follow-up MRI, min	23.5±15.9	31.0±20.5	0.2304
Laboratory data			
HbA1C, %	6.0±0.5	5.6±0.4	0.9745
Glucose, mg/dL	135.8±33.1	137.7±35.2	0.8395
C-reactive protein, mg/dL	0.5±1.4	0.8±1.4	0.2864
Leucocytes, /μL	7371.3±3626.8	7189.4±2832.4	0.6467
Erythrocytes, ×10 000/μL	423.7±70.4	411.1±53.1	0.5940
Platelets, ×10 000/μL	18.3±5.4	20.3±5.7	0.2676
Creatinine, mg/dL	0.8±0.2	1.0±0.9	0.4951
PT-INR	1.1±0.2	1.1±0.2	0.2630
D-dimer, μg/mL	1.8±1.7	2.3±2.0	0.6933
M1 SVS	1 (6.3%)	2 (6.1%)	0.9999
Site of occlusion			
ICA	2 (12.5%)	6 (18.2%)	0.6138
M1	8 (50.0%)	18 (54.5%)	0.7650
M2	6 (37.5%)	9 (27.3%)	0.4663
Ischemic volume, mL	28.1±30.5	20.9±27.8	0.2566

PT-INR indicates prothrombin time international normalized ratio; SVS, susceptibility vessel sign; ICA, internal carotid artery.

M1 SVS was more frequent in the no early recanalization group than in the early recanalization group (31.3% versus 6.1%, $P=0.0007$). Although 89.7% of patients with M1 SVS had no early recanalization, 55.3% of patients without the M1 SVS sign had no early recanalization ($P=0.0007$; Figure 2). There were no significant differences in the other clinical characteristics between the 2 groups.

Eight variables identified on univariate analysis at $P<0.2$ were selected. The area under receiver operating characteristic curves analysis yielded cutoff levels predicting no early recanalization with high sensitivity and high specificity as follows: time to stroke onset to treatment ≥140 minutes (sensitivity of 59.0% and specificity of 55.1%) and glucose ≥135 mg/dL (54.2% and 51.0%). Multivariate logistic regression analysis revealed that M1 SVS was the only independent factor associated with no early recanalization (OR, 7.157; 95% CI, 1.756 to 29.1721; $P=0.0060$; Table 3). Sensitivity, specificity, positive predictive value, and negative predictive value of M1 SVS for predicting no early recanalization were 31.3%, 93.9%, 89.7%, and 44.7%, respectively.

Discussion

M1 SVS was the only independent factor associated with no recanalization after tPA administration. The positive predic-

Table 2. Clinical Characteristics and MRI Findings Before Tissue-Type Plasminogen Activator Infusion Between Patients With Early Recanalization and Nonearly Recanalization

Clinical Symptoms, %	All Patients (N=132)	Early Recanalization (N=49)	No Early Recanalization (N=83)	*P*
Female	69 (52.3%)	24 (49.0%)	45 (54.2%)	0.5606
Age, y	76.4±10.2	76.3±10.4	76.5±10.2	0.9737
Hypertension	84 (63.6%)	31 (63.3%)	53 (63.9%)	0.9457
Diabetes mellitus	28 (21.2%)	8 (16.3%)	20 (24.1%)	0.2914
Hyperlipidemia	24 (18.2%)	7 (14.3%)	17 (20.5%)	0.3725
Smoking	36 (27.1%)	15 (30.6%)	21 (25.0%)	0.4822
Atrial fibrillation	85 (64.4%)	28 (57.1%)	57 (68.7%)	0.1813
Stroke type				
Cardioembolic stroke	87 (65.9%)	29 (59.2%)	58 (70.0%)	0.2104
Large artery disease	9 (6.8%)	1 (2.0%)	8 (9.6%)	0.1529
Use of antiplatelet therapy				
Warfarin	15 (11.4%)	3 (6.1%)	12 (14.5%)	0.1449
Aspirin	33 (25.0%)	13 (26.5%)	20 (24.1%)	0.7550
National Institutes of Health Stroke Scale score	15.5±6.8	15.2±6.3	15.6±7.0	0.6993
Systolic blood pressure, mm Hg	150.9±22.2	150.8±20.8	150.9±23.1	0.7577
Diastolic blood pressure, mm Hg	83.0±15.3	81.3±16.0	84.0±14.9	0.3130
Time from symptom onset to treatment, min	141.4±30.1	134.5±31.9	145.5±28.4	0.0541
Time from end of tissue plasminogen activator infusion to follow-up MRI, min	30.4±26.7	28.4±19.2	31.5±30.1	0.9228
Laboratory data				
HbA1C, %	5.7±1.0	5.6±0.5	5.8±1.2	0.7302
Glucose, mg/dL	150.6±54.9	137.1±34.2	158.6±63.0	0.0400
C-reactive protein, mg/dL	0.6±1.3	0.7±1.4	0.6±1.3	0.9268
Leucocytes, /μL	6980.0±2596.7	7248.8±3076.7	6821.4±2272.0	0.7829
Erythrocytes, ×10 000/μL	417.3±65.0	415.2±58.9	418.5±68.6	0.6993
Platelets, ×10 000/μL	19.6±5.2	19.6±5.6	19.6±5.0	0.8672
Creatinine, mg/dL	0.9±0.7	0.9±0.8	0.9±0.6	0.8524
PT-INR	1.1±0.2	1.1±0.2	1.1±0.2	0.4887
D-dimer, μg/mL	3.1±6.1	2.2±2.0	3.7±7.5	0.6599
M1 SVS	29 (22.0%)	3 (6.1%)	26 (31.3%)	0.0007
Site of occlusion				
ICA	37 (28.0%)	8 (16.3%)	29 (34.9%)	0.0214
M1	58 (43.9%)	26 (53.1%)	32 (38.6%)	0.1047
M2	37 (28.0%)	15 (30.6%)	22 (26.5%)	0.6118
Ischemic volume, mL	30.1±58.9	23.2±28.5	34.4±71.7	0.8454

PT-INR indicates prothrombin time international normalized ratio; SVS, susceptibility vessel sign; ICA, internal carotid artery.

tive value of M1 SVS for predicting no early recanalization was 89.7%.

The magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi may result in hypointense signals on T2*-weighted gradient echo imaging (GRE). Cho et al[16] reported that red thrombi in occluded vessels were visualized as hypointense signals within vascular cisterns on T2*. They called such radiological findings the "GRE susceptibility vessel sign (GRE SVS)." The GRE SVS may reflect thrombus composition. Hemoglobin desaturation from oxyhemoglobin to deoxyhemoglobin occurs within a few hours. Thus, in hyperacute clot cases, the main component may still be oxyhemoglobin, and such emboli would not be identified as GRE SVS on T2*. In other words, the GRE SVS is present in older thrombi, which may be resistant to tPA therapy.

Zangerle et al[7] reported that recanalization was infrequent in patients with diabetes. The present finding showed that the glucose level before tPA infusion but not HbA1c was higher in the no early recanalization group than in the early recanalization group. Therefore, the blood glucose level, rather than the presence or absence of diabetes, is closely associated with no early recanalization. These results were compatible

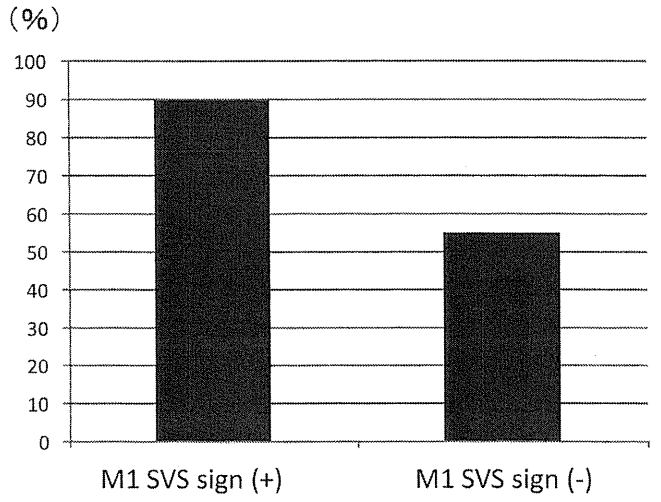

Figure 2. Frequency of no early recanalization after tPA administration between patients with and without M1 SVS (89.7% versus 55.3%; $P=0.0007$). tPA indicates tissue-type plasminogen activator; SVS, susceptibility vessel sign.

with those of a previous report.[15] However, the multivariate regression model did not reveal that blood glucose level was an independent factor associated with no early recanalization. Molina et al[14] reported that early recanalization was more frequent in patients with cardioembolic stroke compared with other stroke types. In fact, patients with cardioembolic stroke more frequently had early recanalization than those with large artery diseases, but the difference was not significant (33.3% versus 11.1%, $P=0.2653$). Using our univariate analysis, ICA occlusion was more frequent in the no early recanalization group than in the early recanalization group. Several investigators reported that tPA was not effective in patients with ICA occlusion.[2,18] The reason for this was that the embolus responsible for ICA occlusion was larger than that responsible for other arterial occlusions, and such an embolus was likely to be resistant to tPA. However, the multivariate regression model did not identify ICA occlusion as an independent factor associated with no early recanalization.

Recently, the REcanalisation using Combined intravenous Alteplase and Neurointerventional ALgorithm for acute Ischemic StrokE (RECANALISE) study demonstrated that the combined intravenous tPA and endovascular approach group had higher recanalization than the only intravenous tPA therapy group in patients with stroke within 3 hours of onset.[21] However, early neurological improvement and favorable outcome were not different between the 2 groups. A better clinical outcome was associated with recanalization in the 2 groups and time to recanalization in the combined intravenous tPA and endovascular approach group. Therefore, time to recanalization appears to be most important for patient outcome. If we can identify patients who will fail tPA before tPA infusion, it may be better to start with endovascular therapy in such patients to achieve earlier recanalization of the occluded artery. Therefore, in patients with acute stroke within 3 hours of onset, M1 SVS may be a sign for endovascular therapy instead of intravenous tPA as first-line therapy.

Table 3. Multivariate Logistic Regression Analysis for Factors Associated With No Early Recanalization

	OR	95% CI	P
Atrial fibrillation	1.332	0.558–3.181	0.5183
Time from stroke onset to treatment ≥140 min	2.117	0.973–4.870	0.0582
Use of warfarin	2.181	0.518–9.189	0.2880
Glucose ≥135 mg/dL	1.243	0.567–2.728	0.5868
Large artery disease	8.448	0.833–85.672	0.0710
ICA occlusion before tPA infusion	0.928	0.279–3.092	0.9037
M1 occlusion before tPA infusion	0.732	0.300–1.786	0.4935
M1 susceptibility vessel sign	7.157	1.756–29.172	0.0060

ICA indicates internal carotid artery; tPA, tissue-type plasminogen activator; OR, odds ratio; CI, confidence interval.

The present study had several limitations. First, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis.[22] Second, MRI cannot be performed in patients with implanted metallic materials such as pacemakers and metal clips; 4 patients were excluded from our study. Third, there are potential pitfalls of the use of SVS on T2*. Blood clots of acute, subacute, and chronic stage can appear as signal loss on T2* because any paramagnetic substance including deoxyhemoglobin, intra- and extracellular methemoglobin, and hemosiderin can appear hypointense on T2*. Therefore, fresh clots seem to be indistinguishable from flowing blood.[23] Thus, when the presence of M1 SVS is identified, ICA or M1 occlusion must be confirmed by MRA to distinguish fresh clots from blood flow. In the present study, to exclude those potential pitfalls, we always used MRA to confirm the occluded artery. Finally, the sample size was small. A larger sample size is needed to confirm these results.

In conclusion, of clinical and MRI factors before tPA infusion, M1 SVS on T2* is the only independent factor associated with no early recanalization within 1 hour after tPA administration. In patients with M1 SVS who are unlikely to respond to tPA therapy, we may consider therapeutic strategies such as combined intravenous tPA and endovascular therapy or endovascular therapy alone instead of intravenous tPA as first-line therapy.

Disclosures

None.

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A simple clinical and MRI scale to predict good outcome in t-PA patients

Kazumi Kimura, Yuki Sakamoto, Yasuyuki Iguchi, Kensaku Shibazaki, Masao Watanabe, Junya Aoki, Takeshi Inoue, Junichi Uemura

Department of Stroke Medicine, Kawasaki Medical School, Kurashiki City, Okayama, Japan

Background and purpose: The frequency of good outcome at 3 months after tissue plasminogen activator (t-PA) therapy is ~35%. The present study aimed to devise a simple scale to predict good outcome using clinical factors and magnetic resonance imaging (MRI) findings before and immediately after t-PA infusion.
Methods: Consecutive patients with acute ischemic stroke treated with t-PA within 3 hours of stroke onset were studied prospectively. We assessed clinical factors independently associated with good outcome [modified Rankin scale (mRS): 0–1] at 3 months after t-PA therapy. We created a simple scale to predict good outcome in t-PA patients using factors selected by multivariate logistic regression analysis.
Results: Subjects comprised 105 patients (69 men; median age, 74 years). Multivariate logistic regression analysis revealed the following independent factors associated with good outcome: baseline National Institutes of Health Stroke Scale (NIHSS) <11 [odds ratio (OR), 13.64; 95% confidence interval (CI), 3.588–51.822; P=0.0001], glucose <150 mg/dl (OR, 3.76; 95%CI, 1.014–13.963; P=0.0475), and early recanalization within 1 hour after t-PA infusion (OR, 5.28; 95%CI, 1.179–23.656; P=0.0296). Those three variables were selected for use in the good outcome scale, with NIHSS <11 as 2 points, glucose <150 mg/dl as 1 point, and early recanalization as 1 point. Frequencies of patients with good outcome for each score were as follows: score 0, 0.0%; score 1, 7.1%; score 2, 43.5%; score 3, 65.4%; and score 4, 71.4%. The C statistic for the score was 0.849 (95%CI, 0.776–0.922).
Conclusion: A simple clinical and MRI scale can predict good outcome in t-PA patients.

Keywords: Acute stroke, Tissue plasminogen activator (t-PA), Good outcome, MRA, Scale

Introduction

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke.[1] The frequency of good outcome [modified Rankin scale (mRS): 0–2] at 3 months after t-PA therapy is ~50%.[1–6] The following factors are reportedly associated with good outcomes: younger age, female sex, low glucose level on admission, and absence of severe neurological deficits.[4,7,8] Furthermore, early arterial recanalization is also associated with good outcome.[9–11] Conversely, poor outcomes are associated with older age, high acute blood pressure, neurological severity, hyperglycemia, activated protein C, no early recanalization of occluded artery, large ischemic lesions on computed tomography (CT) or magnetic resonance imaging (MRI) before t-PA infusion, and the internal carotid artery (ICA) occlusion.[1,4–6,12–21]

Compared to CT, MRI before and immediately after t-PA infusion can provide more information, such as site of arterial occlusion, size of ischemic lesions, and early recanalzation, which has been strongly associated with good outcome after t-PA therapy. To the best of knowledge, there is not a scale for predicting patient outcomes after t-PA therapy using MRI findings. The present study aimed to devise a simple scale for predicting good outcomes at 3 months after t-PA therapy using clinical factors and MRI findings before and immediately after t-PA infusion.

Correspondence to: K Kimura, Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan. Email: kimurak@med.kawasaki-m.ac.jp

Subjects and Methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 hours of stroke onset between October 2006 and November 2009 were studied prospectively. Patients with mRS score >1 before t-PA administration were excluded from the study. The following clinical data were collected from all patients: (1) patient age and gender; (2) time from symptom onset to treatment; (3) arterial blood pressure before t-PA infusion; (4) National Institutes of Health Stroke Scale (NIHSS) score before t-PA infusion; (5) Alberta Stroke Programme Early

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CT Score on diffusion-weighted imaging (DWI-ASPECTS) before t-PA infusion; (6) presence of arterial occlusion on MRA before t-PA infusion; (7) presence or absence of recanalization of occluded arteries within 60 minutes after t-PA administration; (8) vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking; (9) stroke subtype;[22] and (10) laboratory parameters including glucose before t-PA infusion. Inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial.[6]

Before t-PA infusion, all patients underwent MRI studies, including DWI and magnetic resonance angiography (MRA) to identify the occluded arteries. Next, follow-up MRA was performed within 60 minutes after the end of t-PA administration to identify the presence or absence of recanalization in the occluded arteries. MRI was performed using a commercially available echo planar instrument operating on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA).

Recanalization was graded as follows: (1) complete recanalization, reappearance of entire occluded artery and distal branch of vessels; (2) partial recanalization, restoration of part of the distal vessel supplied by an occluded artery; or (3) no recanalization, persistent occlusion. The positive group for recanalization showed partial or complete recanalization within 60 minutes after t-PA infusion, while the negative recanalization group showed no recanalization.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment criteria[22] to determine stroke subtype. Large-vessel disease was defined as >50% arterial stenosis or occlusion corresponding to neurological deficits in the absence of a source of cardiac embolism. Cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Lacunar stroke was defined as the presence of infarction <15 mm, with no source of cardiac embolism and >50% arterial stenosis. Undetermined stroke was used when no etiological source of emboli could be identified.

Statistical analysis was performed using StatView version 5 statistical software to establish associations among clinical factors and patient outcomes at 3 months after t-PA therapy. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann–Whitney *U* test and Kruskal–Wallis *U* test for continuous variables. All data were unadjusted and values of $P<0.05$ were considered significant. Good and poor outcomes at 3 months after t-PA therapy were defined as mRS 0–1 and 2–6, respectively. Multivariate logistic regression analysis was performed to determine factors independently associated with good outcome using variables identified from univariate analysis at a level of $P<0.2$. Cut-off values for continuous variables were determined using area under receiver–operator curves (ROCs). We chose independent variables on multivariate logistic regression analysis and devised the good outcome scale score. Area under ROC (C statistics) and 95% confidence intervals (CIs) were calculated as a measure of predictive ability. Ideal prediction produces a C statistic of 1.00, whereas prediction no better than chance is associated with a C statistic of 0.500.

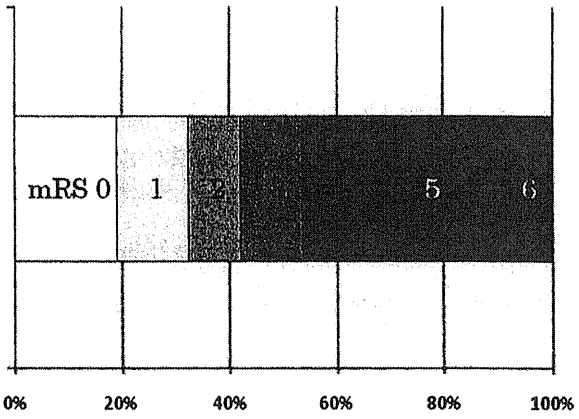

Figure 1 mRS score at 3 months after t-PA therapy.

Results

A total of 144 consecutive stroke patients were treated with t-PA. Two patients were excluded because they had a pacemaker. One patient did not undergo MRI before t-PA infusion due to a lack of time for the MRI study. A total of 36 patients had mRS score >1 before t-PA therapy. As a result, 105 patients (69 men and 36 women; mean age, 72.3±10.9 years; median age, 74 years) were enrolled in the present study. On initial MRA, 22 patients showed no arterial occlusion, 22 had ICA occlusion, 35 had M1 occlusion, 18 had M2 occlusion, 5 had basilar artery occlusion, and 3 had posterior cerebral artery occlusion. The durations between door to MRI study and between symptom onset and t-PA bolus were 18.0±13.2 and 141.4±31.5 minutes.

At 3 months after t-PA therapy, 20 patients had mRS 0, 14 had mRS 1, 10 had mRS 2, 12 had mRS 3, 15 had mRS 4, 26 had mRS 5, and 8 had mRS 6. Therefore, 34 patients had good outcome (mRS 0–1) (Fig. 1). Table 1 shows clinical characteristics of patients with mRS 0–1 and 2–6. Baseline NIHSS score was lower in patients with mRS 0–1 than in those with mRS 2–6 (7.8±4.0 versus 16.9±6.8; $P<0.0001$). Atrial fibrillation (AF) was less frequently observed in patients with mRS 0–1 than in those with mRS 2–6 (32.4% versus 54.9%; $P=0.0302$). Six (12%) of 50 patients with AF were treated with warfarin, but any patients without AF were not treated with warfarin.

Glucose level before t-PA infusion tended to be lower in patients with mRS 0–1 than those with mRS 2–6 (138.5±31.9 versus 151.8±43.0; P=0.0547). Baseline DWI-ASPECTS tended to be higher in patients with mRS 0–1 than in those with mRS 2–6 (8.8±1.4 versus 7.7±2.5; P=0.0543). ROC analysis yielded cut-off levels predicting mRS 0–1 with high sensitivity and high specificity as follows: age <70 years; NIHSS <11; glucose 150 mg/dl; Cr<1.0; and DWI-SAPECT >5. No occlusion on initial MRA or before t-PA infusion was more frequently observed in patients with mRS 0–1 than in those with mRS 2–6 (no occlusion: 38.2% versus 12.7%; P=0.0026). Of 83 patients with occluded artery, early recanalization within 1 hour after t-PA infusion was more frequently observed in mRS 0–1 than in mRS 2–6 [66.7% (14/21) versus 33.9% (21/62); P=0.0085]. ICA occlusion was less frequently observed in patients with mRS 0–1 than in those with mRS 2–6 (5.9% versus 28.2%; P=0.0086). Other factors showed no significant difference between patients with mRS 0–1 and 2–6.

We selected 12 variables, including information before and within 1 hour after t-PA infusion, identified from univariate analysis at P<0.2. Multivariate logistic regression analysis revealed independent factors associated with patients with mRS 0–1 as follows: baseline NIHSS <11 (OR, 13.64; 95%CI, 3.588–51.822; P=0.0001); glucose <150 mg/dl (OR, 3.76; 95%CI, 1.014–13.963; P=0.0475), and early recanalization within 1 hour after t-PA infusion (OR, 5.28; 95%CI, 1.179–23.656; P=0.0296) (Table 2). We chose these three variables for use in the good outcome scale score. When a patient was positive for a variable, we assigned NIHSS <11 as 2 points, glucose <150 mg/dl as 1 point, and recanalization

Table 1 Clinical characteristics of patients

	mRS 0–1 n=34	mRS 2–6 n=71	P
Age (years)	70.8±10.6	73.0±11.1	0.4595
<71	13 (38.2%)	26 (36.6%)	0.8726
Female	8 (23.5%)	28 (39.4%)	0.1081
Hypertension	23 (67.6%)	42 (59.2%)	0.4018
Diabetes mellitus	9 (26.5%)	13 (18.3%)	0.3363
Hyperlipidemia	11 (32.4%)	14 (19.7%)	0.1549
Smoking	18 (52.9%)	30 (42.3%)	0.3636
Atrial fibrillation	11 (32.4%)	39 (54.9%)	0.0302
Time from onset to treatment (minutes)	139.2±31.9	142.5±31.5	0.6004
Baseline NIHSS score	7.8±4.0	16.9±6.8	<0.0001
<11	27 (79.4%)	14(19.7%)	<0.0001
Systolic blood pressure (mmHg)	156.9±23.4	153.6±18.7	0.61.5
Diastolic blood pressure (mmHg)	84.2±16.2	83.1±14.2	0.5994
Glucose (mg/dl)	138.5±38.7	151.8±43.0	0.0547
<150 mg/dl	25 (73.5%)	38 (53.5%)	0.0502
HbA1C (%)	5.8±0.8	5.7±0.8	0.3902
Total cholesterol (mg/dl)	198.4±41.0	191.5±34.7	0.3325
Leucocytes (/μl)	6858.8±2526.0	6854.5±2604.6	0.9645
Erythrocytes (×10 000/μl)	443.6±59.4	427.0±64.0	0.4533
Platelets (×10 000/μl)	19.5±4.4	19.2±5.5	0.4721
Creatinine (mg/dl)	1.052±1.0	0.78±0.21	0.1730
<1.0	26 (76.5%)	61 (85.9%)	0.2295
Stroke type			
Cardioembolic stroke	13 (38.2%)	40 (56.3%)	0.1805
Large artery diseases	2 (5.9%)	3 (4.2%)	0.7091
Lacunar Stroke	3 (8.8%)	1 (1.4%)	0.0913
Undetermined stroke	16 (47.1%)	27 (38.0%)	0.3786
Baseline DWI-ASPECTS	8.8±1.4	7.7±2.5	0.0543
>5	32 (94.1%)	49 (69.0%)	0.0053
No occlusion on MRA before t-PA infusion	13 (38.2%)	9 (12.7%)	0.0026
Site of occlusion			
ICA	2 (5.9%)	20 (28.2%)	0.0086
M1	10 (29.4%)	25 (35.2%)	0.5553
M2	6 (17.6%)	12 (16.9%)	0.9244
BA	1 (2.9%)	4 (5.6%)	0.5443
PCA	2 (5.9%)	1 (1.4%)	0.2444
ICH on T2* 24 hours after t-PA infusion	7 (21.2%)	25 (40.3%)	0.0606
Symptomatic ICH	0 (%)	1 (1.5%)	0.4869
Recanalization within 1 hour after t-PA infusion	14/21 (66.7%)	21/62 (33.9%)	0.0085

Note: mRS, modified Rankin scale; NIHSS, National Institutes of Health Scale Score; DWI-ASPECTS, Alberta Stroke Programme Early CT Score on diffusion-weighted imaging; MRA, magnetic resonance angiography; t-PA, tissue plasminogen activator; ICA, internal carotid artery; BA, basilar artery; PCA, posterior cerebral artery; ICH, intracranial hemorrhage.
*Excluding the 11 patients with PCA and BA occlusion.

within 1 hour after t-PA infusion as 1 point according to OR on multivariate logistic regression analysis, for a possible total of 4 points (Table 3). The relationship between good outcome scale score and frequency of patients with mRS 0–1 is shown in Fig. 2. Frequencies of good outcome patients for each score were as follows: 0.0% of 21 patients with good outcome scale score 0, 7.1% of 28 patients with score 1, 43.5% of 23 patients with score 2, 65.4% of 26 patients with score 3, and 71.4% of 7 patients with score 4. As good outcome scale score increased, patients with mRS 0–1 became more frequent. C statistic of score was 0.849 (95%CI, 0.776–0.922).

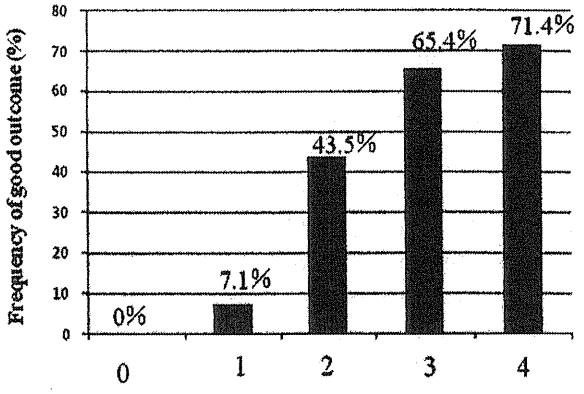

Figure 2 Relationship between a simple scale score and frequency of good outcome (mRS score 0–1) at 3 months after t-PA therapy.

Discussion

The present study demonstrated that NIHSS score <11, glucose <150 mg/dl, and early recanalization within 1 hour after t-PA infusion were factors independently associated with good outcome 3 months after t-PA therapy using multivariate logistic regression analysis. We devised a simple scale to predict good outcome. The C statistic for present score was very high, at 0.849. We thus believe that a simple score is useful to predict good outcomes after t-PA therapy.

Previous studies have reported that good outcome 3 months after t-PA therapy was associated with younger age and lower NIHSS score before t-PA infusion.[4,7] Conversely, poor outcome was associated with hyperglycemia, high acute blood pressure, lower ASPECTS on CT or MRI, severe neurological deficits, and ICA occlusion before t-PA infusion.[1,4–6,12–18] The present results except for high blood pressure were compatible with previous findings. The effect of emergent IV antihypertensives on stroke outcome is a matter of contention. Martin-Schild *et al.*[23] reported that lowering blood pressure before intravenous t-PA therapy was not associated with poor outcomes.

In the present study, the use of multivariate logistic regression analysis revealed baseline NIHSS <11 as a factor independently associated with good outcome, and the OR was approximately 14, which was the highest among the factors examined. We therefore assigned NIHSS <11 as 2 points. Even if treatment with t-PA is provided, patients with severe neurological deficit as measured by NIHSS score were more likely to experience poor outcomes. Frankel *et al.*[24] reported that approximately 75% of patients with NIHSS >17 at baseline showed poor outcomes. In fact, in our study, all patients (100%) with baseline NIHSS >17 had poor outcomes (mRS >1). Conversely, patients with slight neurological deficit were more likely to have good outcomes. In the present study, 27 of 41 patients (66%) with baseline NIHSS <11 experienced good outcomes (mRS 0–1). Patient outcomes should be most affected by initial ischemic damage before t-PA infusion.

Molina *et al.*[11] reported maltimodel outcome score for stroke thrombolysis. Their factors included NIHSS score, CT-ASPECTS value, proximal occlusion, blood pressure, and early recanalzation. Therefore, NIHSS score, and recanalzation were the same as our score. But in our study, multivariate

Table 2 Multivariate logistic regression analysis for factors associated with patients with mRS 0–1

	OR	95%CI	*P*
Age <70 years	0.50	0.150–1.672	0.2609
Female	0.37	0.107–1.298	0.1209
Hyperlipidemia	2.44	0.590–10.069	0.2181
Atrial fibrillation	0.71	0.087–5.897	0.7580
Baseline NIHSS score <11	13.64	3.588–51.822	0.0001
Glucose <150 mg/dl	3.76	1.014–13.963	0.0475
Cardioembolic stroke	1.73	0.222–13.404	0.6018
Lacunar stroke	1.52	0.107–21.463	0.7587
DWI-ASPECTS >5	1.921	0.290–12.703	0.4982
No occlusion on MRA before t-PA infusion	4.67	0.746–29.140	0.0997
No ICA occlusion before t-PA infusion	1.73	0.324–9.250	0.5208
Recanalization within 1 hour after t-PA infusion	5.28	1.179–23.656	0.0296

Note: OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Scale Score; DWI-ASPECTS, Alberta Stroke Programme Early CT Score on diffusion-weighted imaging; MRA, magnetic resonance angiography; t-PA, tissue plasminogen activator; ICA, internal carotid artery.

logistic regression analysis did not reveal that DWI-ASPECTS value and blood pressure were independent factors for good outcome. Interestingly, our study demonstrated glucose <150 mg/dl as an independent factor associated with good outcomes. Hyperglycemia on admission is reportedly associated with a poor recanalization rate for the occluded artery and increased risk of death, symptomatic intracranial hemorrhage, and poor functional status.[17,18] However, in the present study, patients with glucose ≥150 mg/dl did not show less frequent recanalization of the occluded artery than those with glucose <150 mg/dl (43.1% versus 40.6%; P=0.9999). Asymptomatic intracranial hemorrhage on T2* at 24 hours after t-PA infusion tended to be less frequently observed in patients with glucose <150 mg/dl than in those with glucose ≥150 mg/dl (25.8% versus 37.2%; P=0.2119), but this difference was not significant. Nevertheless, 30 of 42 patients (71.4%) with glucose >150 mg/dl had poor outcomes (mRS >2). Hyperglycemia appears to contribute to poor outcomes, although the underlying mechanisms remain unclear.

Early arterial recanalization is a marker of good outcome after t-PA infusion.[9–11] Evaluation of early arterial recanalization thus appears important for predicting good outcome. In the present study, MRA rather than transcranial Doppler was used to evaluate the presence of recanalization of occluded arteries, as several cases of elderly female and/or Asian patients with an insufficient temporal bone window have been described.[25] If a patient has a sufficient temporal bone window, transcranial Doppler is preferable to MRA as a convenient tool for evaluating the recanalization of occluded arteries.

The present study displayed several limitations. First, the use of MRA is somewhat inaccurate for detecting vessel occlusion or stenosis.[26] Second, MRI cannot be performed in patients in whom metallic materials, such as pacemakers and metal clips, have been implanted. Two such patients were excluded from the present study. Third, rates of recanalization may have been lower because the dose of t-PA (0.6 mg/kg)[6] is lower in Japan than the internationally approved dosage of 0.9 mg/kg. However, recently, Mori *et al.*[27] reported the dosage efficacy of 0.6 mg/kg including potential for early recanalization of occluded cerebral artery compared to internationally approved dosage of 0.9 mg/kg in acute ischemic stroke. Finally, the sample size was small. A large study should be needed to confirm our score.

Table 3 Components of the good outcome scale

Score		
Baseline NIHSS score <11	Yes=2	No=0
Recanalization within 1 h after t-PA infusion	Yes=1	No=0
Glucose <150 mg/dl	Yes=1	No=0
Total	4 points	

Note: NIHSS, National Institutes of Health Scale Score; t-PA, tissue plasminogen activator.

In conclusion, a simple score can be used to predict good outcome in t-PA patients. We assigned NIHSS <11 as 2 points, glucose <150 mg/dl as 1 point, and early recanalization as 1 point, for a possible total of 4 points. The C statistic for the score was high at 0.849 (95%CI, 0.776–0.922). We should predict patient outcome at 3 months using the present score immediately after t-PA therapy. However, our score was developed and tested in the same dataset. Therefore, we should need a prospective study to confirm the accuracy of this score.

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Recanalization within One Hour after Intravenous Tissue Plasminogen Activator Is Associated with Favorable Outcome in Acute Stroke Patients

Kazumi Kimura Yasuyuki Iguchi Kensaku Shibazaki Junya Aoki
Masao Watanabe Kazuto Kobayashi Yuki Sakamoto

Department of Stroke Medicine, Kawasaki Medical School, Kurashiki City, Japan

Key Words
Tissue plasminogen activator · Magnetic resonance angiography · Acute stroke · Recanalization, outcome

Abstract
Background/Aim: Early recanalization after tissue plasminogen activator (t-PA) infusion greatly improves outcome in stroke patients. However, the time threshold of early recanalization for a favorable outcome remains unclear. The aim of this study was to assess patient outcome 3 months after t-PA therapy among patients with early, delayed and without recanalization. ***Methods:*** Consecutive patients with major brain artery occlusion on magnetic resonance angiography (MRA) before t-PA infusion were enrolled. We divided the patients into 3 groups according to the findings of follow-up MRA 1 and 24 h after t-PA: the early group who had recanalization within 1 h after t-PA; the delayed group who had recanalization between 1 and 24 h, and the no recanalization group. We then assessed the outcomes (modified Rankin score 0–1) 3 months after t-PA therapy among the 3 groups. ***Results:*** A total of 92 patients (53 men, mean age 75.8 ± 10.3 years) were enrolled. A favorable outcome was most frequently observed in the early group (n = 39, 40.6%), followed by the delayed group (n = 25, 18.2%), and the no recanalization group (n = 28, 10.5%; p = 0.037). After adjusting for age, atrial fibrillation and NIHSS score, the adjusted OR for early recanalization when compared with no recanalization was 7.11 (95% CI 1.177–43.063; p = 0.032) for a favorable outcome, while the adjusted OR for delayed recanalization was 1.75 (95% CI 0.104–29.356; p = 0.698). ***Conclusion:*** Early recanalization within 1 h after intravenous t-PA is associated with a favorable outcome in stroke patients.

The intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in acute ischemic stroke patients [1, 2]. Early recanalization after t-PA infusion greatly improves patient outcome. However, the time threshold of early recanalization and favorable outcome remains unclear.

The ischemic penumbra is the brain region surrounding the ischemic core that receives limited blood supply from collateral circulation [3]. When the occluded artery is not recanalized, the penumbra surrounding the ischemic core and neurological deficit worsen with time [4]. However, when the occluded artery is recanalized within a limited time window and cerebral blood flow is normalized, the ischemic penumbra may recover without defect. Therefore, the ischemic penumbra is considered to be the target for t-PA therapy. We hypothesized that earlier re-

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Dr. Kazumi Kimura
Department of Stroke Medicine, Kawasaki Medical School
577 Matsushima, Kurashiki City
Okayama 701-0192 (Japan)
Tel. +81 86 462 1111, Fax +81 86 464 1128, E-Mail kimurak@med.kawasaki-m.ac.jp

canalization after t-PA therapy would result in better outcome in acute stroke patients. The aim of this study was to assess patient outcome 3 months after t-PA therapy among patients with early recanalization (within 1 h after t-PA infusion), delayed recanalization (1–24 h after t-PA infusion) and without recanalization.

Methods

Consecutive acute ischemic stroke patients treated with t-PA within 3 h of stroke onset between October 2006 and October 2009 were prospectively studied. Of these, patients who had major brain artery occlusion on baseline magnetic resonance angiography (MRA) before t-PA infusion were enrolled in the present study. The following clinical data were collected from all patients: (1) patient age and sex; (2) time from stroke onset to treatment; (3) arterial blood pressure before t-PA infusion; (4) NIHSS score before and 7 days after t-PA infusion; (5) presence of arterial occlusion on MRA before t-PA infusion; (6) presence or absence of recanalization of occluded arteries within 60 min and 24 h after t-PA administration; (7) initial DWI-ASPECTS [5]; (8) vascular risk factors, including hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL); (9) presence of potential cardiac sources of emboli; (10) stroke subtype [6]; (11) laboratory parameters before t-PA infusion, and (12) modified Rankin score (mRS) 3 months after t-PA therapy. Inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial using CT [7]. t-PA dose was 0.6 mg/kg.

Before t-PA infusion, magnetic resonance imaging (MRI) studies, including diffusion-weighted imaging (DWI), MRA, and T2*, were first performed in order to identify occluded arteries. Then, CT was also performed on all patients immediately after MRI study. Next, follow-up MRA was performed within 1 and 24 h after the end of t-PA administration in order to identify the presence or absence of recanalization in the occluded arteries. T2* was performed in order to assess the presence of cerebral hemorrhage. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded as MRI is contraindicated in such patients. MRI was performed using a commercially available echo planar instrument on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, Wisc., USA).

The presence of large artery occlusion was assessed by MRA. The main occluded arteries in the brain on initial MRA were identified as follows: M1 occlusion; M2 occlusion; internal cerebral artery (ICA) occlusion; posterior cerebral artery (PCA) occlusion, and basilar artery (BA) occlusion. Recanalization was graded as complete, partial, or no recanalization according to our previous criteria, as follows: (1) complete recanalization, reappearance of the entire occluded artery and distal branches; (2) partial recanalization, restoration of some of the distal vessels supplied by the occluded artery, and (3) no recanalization, persistent occlusion. The experienced researchers who evaluated the MRA findings were blinded to patient clinical background and the initial presence of an occluded artery. We divided patients into 3 groups according to the presence or absence of recanalization: the early recanalization group (early group) had recanalization within 1 h after the end of t-PA infusion; the delayed recanalization group (delayed group) had no recanalization within 1 h after t-PA but had recanalization at 24 h after t-PA infusion, and the no recanalization group had no recanalization after t-PA therapy.

A neurologist determined NIHSS scores before, immediately after, and 1 and 7 days after t-PA infusion. Three measures of clinical recovery based on methods modified from those in previous studies were used [8]. A dramatic improvement was defined as a ≥10-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. A good improvement was defined as a ≥4-point reduction in total NIHSS score. Worsening was defined as a ≥4-point increase in total NIHSS score. Favorable and poor outcomes 3 months after t-PA therapy were defined as a mRS of 0–1 and >3 or death, respectively.

Asymptomatic and symptomatic intracranial hemorrhage (ICH) was assessed by MRI T2* 24 h after t-PA infusion. Symptomatic cerebral hemorrhage was defined as an increase in total NIHSS score of ≥4 when cerebral hemorrhage was likely to be the cause of clinical deterioration.

Statistical analysis was performed using StatView version 5 statistical software. We compared clinical characteristics and neurological recovery 7 days after t-PA therapy and patient outcome 3 months after t-PA therapy among the 3 groups. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test and Kruskal-Wallis U test for continuous variables. Values of $p < 0.05$ were considered significant. All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients. The design of the study was approved by the Ethics Committee of Kawasaki Medical School.

Results

A total of 135 consecutive stroke patients received t-PA treatment. Two patients were excluded because they had pacemakers. One patient did not undergo MRI before t-PA infusion because there was insufficient time for the MRI study. We excluded 7 patients who underwent mechanical thrombolysis for the occluded artery 1 h after t-PA infusion. On initial MRA, 33 patients had no arterial occlusion, 28 had ICA occlusion, 35 had M1 occlusion, 19 had M2 occlusion, 7 had BA occlusion, and 3 had PCA occlusion. Thus, 92 patients (53 men, 39 women; mean age 75.8 ± 10.3 years) were enrolled in the present study. The times from symptom onset to door and from door to MRA study were 140.3 ± 32.8 and 62.5 ± 23.8 min, respectively. The baseline NIHSS score was 16.2 ± 7.0.

Recanalization Rate within 1 and 24 h after t-PA Infusion

Follow-up MRA after t-PA infusion showed early recanalization in 39 (42.4%) patients (early group; complete in 13 patients, partial in 26). With regard to the site of oc-

Table 1. Patients' clinical characteristics

	Time of recanalization			
	early recanalization (within 1 h; n = 39)	delayed recanalization (1–24 h; n = 25)	no recanalization (n = 28)	p
Age, years	75.4 ± 9.2	75.1 ± 9.4	76.8 ± 12.6	0.6306
Female, n	17 (44.6%)	7 (28.0%)	15 (53.6%)	0.1673
Hypertension, n	24 (61.5%)	15 (60.0%)	21 (75.0%)	0.4244
Diabetes mellitus, n	5 (12.8%)	2 (8.0%)	10 (35.7%)	0.0168
Hyperlipidemia, n	10 (25.6%)	3 (12.0%)	9 (32.1%)	0.2169
Smoking, n	17 (43.6%)	11 (44.0%)	11 (39.3%)	0.9231
Atrial fibrillation, n	18 (46.2%)	21 (84.0%)	16 (57.1%)	0.0101
NIHSS score				
Baseline	15.3 ± 6.6	16.4 ± 7.3	17.4 ± 7.2	0.4189
1 h after t-PA infusion	11.1 ± 6.6	15.3 ± 7.2	17.1 ± 6.4	0.0065
24 h after t-PA infusion	7.8 ± 6.8	13.4 ± 8.5	17.4 ± 8.8	<0.0001
7 days after t-PA infusion	6.9 ± 8.5	13.4 ± 11.1	19.3 ± 11.6	<0.0001
Baseline DWI-ASPECTS[1]	7.6 ± 2.1	7.4 ± 2.3	6.4 ± 2.6	0.1981
Systolic blood pressure, mm Hg	157.1 ± 22.2	153.9 ± 17.6	156.6 ± 20.8	0.8331
Diastolic blood pressure, mm Hg	82.4 ± 15.0	87.1 ± 14.0	82.1 ± 18.9	0.4494
Glucose, mg/dl	139.4 ± 36.1	149.6 ± 45.1	154.6 ± 47.3	0.3714
Stroke type				0.2013
Cardioembolic stroke	20 (51.3%)	20 (80.0%)	16 (57.1%)	
Large artery diseases	3 (7.7%)	1 (4.0%)	3 (10.7%)	
Undetermined stroke	16 (41.0%)	4 (16.0%)	9 (32.1%)	
Occluded artery				0.3099
ICA	9 (23.1%)	7 (28.0%)	12 (42.9%)	
M1	18 (46.2%)	9 (36.0%)	8 (28.6%)	
M2	9 (23.1%)	6 (24.0%)	4 (14.3%)	
BA	2 (5.1%)	1 (4.0%)	4 (14.3%)	
PCA	1 (2.6%)	2 (8.0%)	0	
Intracranial hemorrhage on T2*				
24 h after t-PA infusion	13 (33.3%)	18 (72.0%)	3 (10.7%)	<0.0001

[1] 10 patients with PCA and BA occlusion were excluded.

clusion, the early recanalization rate was: 9 (32.1%) patients (complete in 1 patient, partial in 8) in ICA occlusion; 18 (51.4%) patients (complete in 6 patients, partial in 12) in M1 occlusion; 9 (47.4%) patients (complete in 5 patients, partial in 6) in M2 occlusion; 2 (28.6%) patients (complete in 1 patient, partial in 1) in BA occlusion, and 1 (33.3%) patient (partial) in PCA occlusion. Therefore, in 82 patients with ICA, M1 and M2 occlusion the complete and partial recanalization rates were 14.6 and 29.3%, respectively. Of 53 patients with an occluded artery within 1 h after t-PA infusion, MRA 24 h after t-PA infusion confirmed delayed recanalization between 1 and 24 h after t-PA infusion in 25 patients (delayed group; complete in 6 patients, partial in 19) and no recanalization in 28 patients (no recanalization group). Of 39 patients in the early group, 1 patient had a re-occluded artery (M1). With regard to the site of occlusion in the delayed group, the delayed recanalization rate was 28.0% in ICA occlusion, 25.7% in M1 occlusion, 31.6% in M2 occlusion, 14.3% in BA occlusion, and 66.7% in PCA occlusion. Table 1 shows the clinical characteristics of the 3 groups.

Neurological Recovery at 1 and 24 h and 7 Days after t-PA Therapy

NIHSS scores immediately, 24 h and 7 days after t-PA were 16.2 ± 7.0, 12.2 ± 8.9, and 12.4 ± 11.4, respectively. Baseline NIHSS scores did not differ among the three groups, but those at 1 and 24 h and 7 days after t-PA therapy were lowest in the early group (table 1).

Dramatic improvement, good improvement, and worsening were observed in 7 (7.6%), 21 (22.8%), and 5 (5.4%) patients immediately after t-PA infusion, in 24

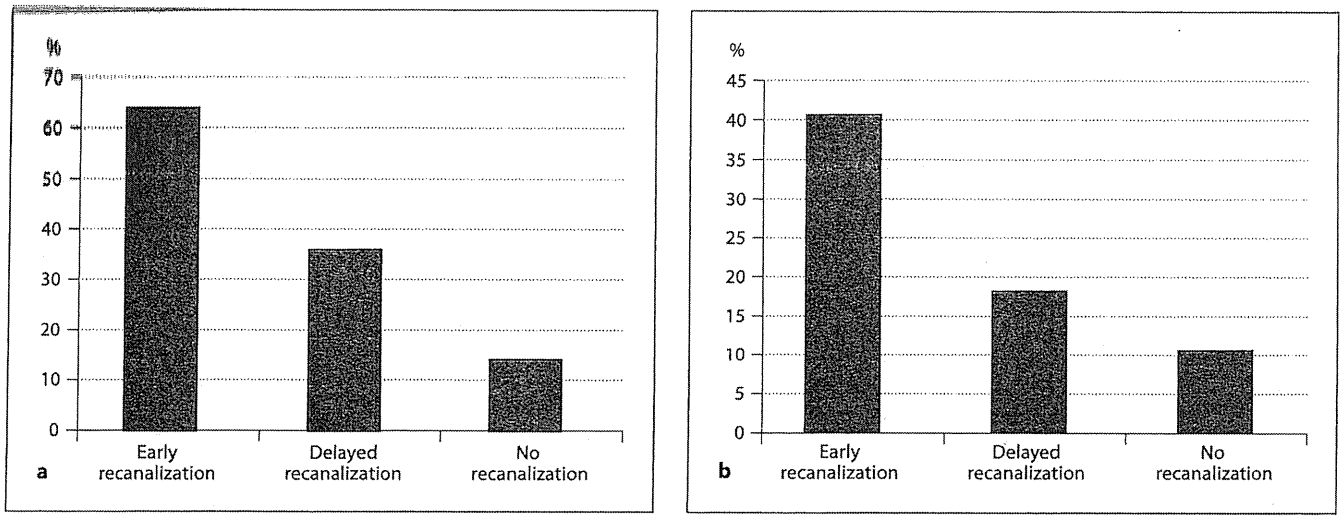

Fig. 1. a Frequency of dramatic recovery 7 days after t-PA therapy. **b** Frequency of an mRS score of 0–1 at 3 months after t-PA therapy.

(26.1%), 26 (28.3%), and 10 (10.9%) patients 24 h after t-PA infusion, and in 38 (41.3%), 18 (19.6%), and 17 (18.5%) patients, respectively, 7 days after t-PA infusion. Dramatic recovery immediately, 24 h, and 7 days after t-PA infusion was most frequent in patients in the early group (fig. 1a; table 2).

Patient Outcomes 3 Months after t-PA Therapy

Three months after t-PA therapy, 19 (20.7%) patients had a favorable outcome, and 56 (60.9%) patients had a poor outcome. A favorable outcome was most frequently observed in the early group (33.3% in early group vs. 16.0% in delayed group vs. 7.1% in no recanalization group; $p = 0.026$), and poor outcome was less frequently seen in the early group (38.5 vs. 68.0 vs. 85.7%, respectively; $p < 0.0001$; table 2).

When 19 patients with baseline mRS scores of >1 were excluded, 26.0% of the patients had a favorable outcome, and 53.4% of the patients had a poor outcome. A favorable outcome was most frequently observed in the early group (40.6% in early group vs. 18.2% in delayed group vs. 10.5% in no recanalization group; $p = 0.0366$) (fig. 1b; table 2), and poor outcome was less frequently seen in the early group (28.1 vs. 63.6 vs. 84.2%, respectively; $p < 0.0001$). The sensitivity and specificity for early recanalization to predict a favorable outcome 3 months after t-PA therapy were 68.4 and 64.8%, respectively. When we calculated the OR for the early and delayed groups, as compared with the no recanalization group, for favorable outcome 3 months after t-PA therapy after adjusting for age (<70 years), AF and NIHSS score (<11) as variables associated with favorable outcome, the adjusted OR of early recanalization was 7.11 (95% CI 1.177–43.063; $p = 0.0326$), but the adjusted OR of delayed recanalization was 1.748 (95% CI 0.104–29.356; $p = 0.6981$).

Cerebral Hemorrhage on T2 24 h after t-PA Infusion*

ICH was observed in 34 (37.0%) patients. Symptomatic ICH within 24 h after t-PA infusion was seen in 2 patients. ICH was most frequently seen in the delayed group (33.3% in early group, 72.0% in delayed group, 10.7% in no recanalization group; $p < 0.0001$).

Discussion

In the present study, approximately 40% of patients with early recanalization had a favorable outcome 3 months after t-PA therapy. On the other hand, of the patients with no recanalization, only 10% had a favorable outcome. After adjusting for age, atrial fibrillation and NIHSS score, the adjusted OR of early recanalization for a favorable outcome was almost 7 when compared with no recanalization. Therefore, early recanalization within 1 h after t-PA infusion is strongly associated with a favorable outcome 3 months after t-PA therapy.

In our patients with ICA, M1 and M2 occlusion, the complete recanalization rate within 1 h after t-PA infu-

Table 2. Neurological recovery of patients

	Time of recanalization			
	early recanalization (within 1 h; n = 39)	delayed recanalization (1–24 h; n = 25)	no recanalization (n = 28)	p
1 h after t-PA infusion				
Dramatic recovery	7 (17.9%)	0 (0%)	0 (0%)	0.006
Good improvement	13 (33.3%)	5 (20.0%)	3 (10.7%)	0.087
Worsening	0 (0%)	1 (4.0%)	4 (14.3%)	0.037
24 h after t-PA infusion				
Dramatic recovery	18 (46.2%)	3 (12.0%)	3 (10.7%)	0.001
Good improvement	12 (30.8%)	7 (28.0%)	7 (25.0%)	0.874
Worsening	1 (2.6%)	3 (12.0%)	6 (21.4%)	0.049
7 days after t-PA infusion				
Dramatic recovery	25 (64.1%)	9 (36.0%)	4 (14.3%)	0.0002
Good improvement	6 (15.4%)	5 (20.0%)	7 (25.0%)	0.618
Worsening	3 (7.7%)	4 (16.0%)	10 (35.7%)	0.013
mRS score 3 months after t-PA therapy	(n = 39)	(n = 25)	(n = 28)	
0–1	13 (33.3%)	4 (16.0%)	2 (7.1%)	0.026
2–3	11 (28.2%)	4 (16.0%)	2 (7.1%)	0.085
4–5	11 (28.2%)	15 (60.0%)	17 (60.7%)	0.009
Death	4 (10.3%)	2 (8.0%)	7 (25.0%)	0.137
mRS score 3 months after t-PA therapy[1]	(n = 32)	(n = 22)	(n = 19)	
0–1	13 (40.6%)	4 (18.2%)	2 (10.5%)	0.037
2–3	10 (31.3%)	4 (18.2%)	1 (5.3%)	0.081
4–5	7 (21.9%)	12 (54.5%)	12 (63.2%)	0.006
Death	2 (6.3%)	2 (9.1%)	4 (21.1%)	0.248

[1] 19 patients with baseline mRS score of >1 were excluded.

sion was 14.6%, and was similar to the results of a control group (18%) in the CLOTBUST study using transcranial Doppler (TCD) [9]. Furthermore, in the DEFUSE study using MRA [10], the complete and partial recanalization rate 3–6 hours after t-PA infusion was 42.8% (18 of 42 patients with ICA and MCA occlusion), which was compatible with our results (43.9%). Therefore, approximately 40% of patients with ICA and MCA occlusion after t-PA therapy should have early recanalization including complete and partial.

Early recanalization within 1 h after t-PA infusion is also associated with a favorable outcome when compared with delayed recanalization between 1 and 24 h after t-PA infusion. During the acute phase of stroke, when an occluded artery is not recanalized, the penumbra surrounding the ischemic core reduces in size over time, becoming an ischemic core [4]. Thus, the infarction area increases with time, resulting in greater neurological deficit. On the other hand, when an occluded artery is recanalized by interventions such as intravenous t-PA therapy, the penumbra area is rescued by reperfusion, thereby reducing the neurological deficit. ICH was most frequently seen in the delayed group, and even if asymptomatic ICH occurs without neurological deterioration, neurological recovery may be disrupted.

In the present study, when excluding 19 patients with a baseline mRS score of >1, only 26% of patients had a favorable outcome (mRS 0–1) 3 months after t-PA therapy. This rate was lower than in previous studies [1, 2, 7]. Our study only included patients with a major occluded artery before t-PA infusion, but not those with no occluded arteries. Therefore, our study included more severe stroke patients when compared with previous studies. In fact, the baseline NIHSS scores in this study were higher than in previous studies [1, 2, 7]. Furthermore, our patients were older than in previous studies [1, 2, 7].

Therefore, a high NIHSS and older age should be associated with a low rate of favorable outcome after t-PA therapy.

In the present study, MRA rather than TCD was used to evaluate the presence of recanalization of occluded arteries, as several cases of elderly female and/or Asian patients with an insufficient temporal bone window have been described [11]. Furthermore, there may be differences between MRA and TCD in their ability to identify the presence of recanalization. MRA can identify the presence of ICA, M1 and M2 occlusion. TCD cannot always diagnose the presence of M2 occlusion, while MRA can accurately detect occluded M2 branches. Therefore, MRA is more sensitive than TCD for the assessment of M2 occlusion and recanalization.

The present study had several limitations. MRA is somewhat inaccurate for the detection of vessel occlusion or stenosis [12]. In addition, MRI cannot be performed in patients with implanted artificial metallic materials, such as pacemakers and metal clips. In fact, 2 such patients were excluded from the present study. Finally, the rates of recanalization may have been lower because the Japanese dose of t-PA (0.6 mg/kg) [7] is lower than the internationally approved dosage of 0.9 mg/kg.

In conclusion, early recanalization within 1 h after i.v. t-PA is a strong predictor of a favorable outcome 3 months after t-PA therapy, but delayed recanalization between 1 and 24 h is not associated with a favorable outcome.

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Early stroke treatment with IV t-PA associated with early recanalization

Kazumi Kimura *, Yasuyuki Iguchi, Kensaku Shibazaki, Junya Aoki, Masao Watanabe, Noriko Matsumoto, Shinji Yamashita

Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan

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ABSTRACT

Purpose: Time from stroke onset to treatment (OTT) is potentially an important factor affecting subsequent outcome in patients treated with t-PA. The aim of the study was to assess the correlation between OTT and early recanalization rate after IV-t-PA therapy.

Methods: Consecutive stroke patients treated with t-PA within 3 h of onset were prospectively studied. Patients with major brain artery occlusion on MRA before t-PA infusion were enrolled. The correlation between OTT and the early recanalization rate within 1 h after t-PA infusion was determined.

Results: 102 patients (M1 occlusion, 41 patients; M2, 19; ICA, 31; BA, 8; and PCA, 3) were enrolled. Follow-up MRA within 1 h after t-PA infusion showed early recanalization in 42 (41.2%) patients (complete in 13 patients, partial in 29). The early recanalization rate was 53.8% with OTT ≤100 min, 57.1% in 101–110 min, 50.0% in 111–120 min, 63.6% in 121–130 min, 33.3% in 131–140 min, 30.0% in 141–150 min, 36.4% in 151–160 min, 18.2% in 161–170 min, and 32.0% in 171–180 min. OTT was negatively correlated with the early recanalization rate ($r=-0.767$, $P=0.0301$). After adjusting the presence of age (>74), ICA occlusion, baseline NIHSS score (<10), and glucose (>150 mg/dl), adjusted OR for early recanalization of OTT ≤130 min against OTT > 130–180 min was 2.97 (95% CI 1.27–6.96, $P=0.012$).

Conclusion: Early recanalization depended on time from stroke onset to IV-t-PA administration. Thus, t-PA should be given to acute stroke patients as soon as possible.

1. Introduction

The intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in acute ischemic stroke patients [1,2]. Early recanalization after t-PA infusion greatly improves patient outcome [3]. However, intravenous thrombolysis using t-PA achieves arterial recanalization in approximately 50% of stroke cases [3–10]. Time from stroke onset to treatment (OTT) is probably an important factor affecting subsequent outcome [11,12]. Marler et al. [12] reported that patients treated with t-PA in 0 to 90 min from stroke onset had increased odds of improvement at 24 h and a favorable 3-month outcome compared to patients treated later than 90 min. In other words, early IV-t-PA treatment should improve patient outcomes. The aim of this study was to assess the correlation between OTT and the early recanalization rate using serial MRA studies.

2. Methods

Consecutive acute ischemic stroke patients treated with t-PA within 3 h of stroke onset between October 2006 and October 2009 were prospectively studied. Of these, the patients who had major brain artery occlusion on baseline MRA before t-PA infusion were enrolled in the present study. The following clinical data were collected from all patients: 1) patient age and sex; 2) time from stroke onset to treatment (OTT); 3) arterial blood pressure before t-PA infusion; 4) NIHSS score before, 24 h, and 7 days after t-PA infusion; 5) presence of arterial occlusion on MRA before t-PA infusion; 6) presence or absence of recanalization of occluded arteries within 60 min after t-PA administration; 7) initial DWI-ASPECTS [13], 8) vascular risk factors, including hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL); 9) presence of potential cardiac sources of emboli; 10) stroke subtype [14], 11) laboratory parameters before t-PA infusion; 12) mRS score at 3 months after t-PA therapy. Inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial [15]. The dose of t-PA was 0.6 mg/kg.

Time of stroke onset was determined by interviewing patients and any available observers present when the symptom was first noticed. If the patient awoke with stroke symptoms, the time of onset was taken as the last time the patient was known to be awake and without any symptoms of stroke. If onset time could not be established with confidence, the patient was not treated with t-PA according to the criteria of the Japan Alteplase Clinical Trial [15], and such patients were excluded from this study. OTT was defined to be the time from stroke onset to the start of t-PA administration. OTT was divided into 9

* Corresponding author. Tel.: +81 86 462 1111; fax: +81 86 464 1128.
E-mail address: kimurak@med.kawasaki-m.ac.jp (K. Kimura).

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subgroups by time: ≤100 min, 101–110 min, 111–120 min, 121–130 min, 131–140 min, 141–150 min, 151–160 min, 161–170 min, and 171–180 min.

Before t-PA infusion, magnetic resonance imaging (MRI) studies, including diffusion-weighted imaging (DWI), MRA, and T2*, were performed to identify the occluded arteries. Next, follow-up MRA was performed within 1 h after the end of t-PA administration to identify the presence or absence of early recanalization in the occluded arteries. T2* was performed to assess the presence of cerebral hemorrhage. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded because MRI is contraindicated in such patients. MRI was performed using a commercially available echo planar instrument on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA).

The presence of large artery occlusion was assessed by MRA. The main occluded arteries in the brain on the initial MRA were identified as follows: M1 occlusion; M2 occlusion; internal cerebral artery (ICA) occlusion; posterior cerebral artery (PCA) occlusion; and basilar artery (BA) occlusion. Recanalization was graded as complete, partial, or no recanalization according to our previous criteria [16], as follows: 1) complete recanalization, reappearance of the entire occluded artery and the distal branches; 2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery; and 3) no recanalization, persistent occlusion. The early recanalization rate within 1 h after the end of t-PA infusion was calculated. The experienced researchers (K.K and Y.I) who evaluated the grade of early recanalization were blinded to patient clinical background. Any disagreement was resolved by consensus. κ statistics were used to assess the researchers' agreement on the grade of early recanalization.

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography (ECG), 24-h ECG monitoring, and transthoracic echocardiography. Transesophageal echocardiography (TEE) was also performed when appropriate. The following potential emboligenic cardiac diseases were considered: atrial fibrillation (AF); acute and previous myocardial infarction; mitral valve disease; and dilated cardiomyopathy. All patients underwent color-flow duplex carotid ultrasonography on the day of admission. Significant arterial stenosis was identified as stenosis >50% or ulcerated plaque in the affected artery that corresponded to the neurological deficits.

A neurologist determined the NIHSS scores before, 1 day, and 7 days after t-PA infusion. The ΔNIHSS score was defined as the initial NIHSS score prior to t-PA thrombolysis minus the NIHSS score 7 days after t-PA infusion. Three measures of clinical recovery based on modified methods used in previous studies were used [17]. "Dramatic improvement" was defined as a ≥10 point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. "Good improvement" was defined as a ≥4 point reduction in the total NIHSS score. "Worsening" was defined as a ≥4 point increase in the total NIHSS score. Favorable and poor outcome at 3 months after t-PA therapy were defined as a mRS 0–2 and >3 or death, respectively.

Asymptomatic and symptomatic intracranial hemorrhage (ICH) was assessed by MRI T2* 24 h after t-PA infusion. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of ≥4 when the cerebral hemorrhage was likely to be the cause of the clinical deterioration.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [18] to determine stroke subtype. Large-vessel disease (LVD) was defined as >50% arterial stenosis or occlusion corresponding to the neurological deficits in the absence of a source of cardiac embolism. A cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Lacunar stroke was defined as the presence of infarction <15 mm and the absence of a source of cardiac embolism and >50% arterial stenosis. When no etiological source of emboli could be identified, the stroke was classified as undetermined.

Statistical analysis was performed using StatView version 5 statistical software. The early recanalization rates were calculated in patients with OTT ≤100 min, 101–110 min, 111–120 min, 121–130 min, 131–140 min, 141–150 min, 151–160 min, 161–170 min, and 171–180 min. Thus, the correlation between the early recanalization rate and the OTT was examined using Spearman's rank correlation. Next, the correlation between OTT and ΔNIHSS score was investigated using the Spearman rank correlation test. Values of $p<0.05$ were considered significant. All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients. The design of the study was approved by the Ethics Committee of Kawasaki Medical School.

3. Results

A total of 138 consecutive stroke patients received t-PA treatment. Two patients were excluded because they had a pacemaker. One patient did not have MRI before t-PA infusion because there was no time for the MRI study. On initial MRA, 33 patients had no arterial occlusion, 31 had ICA occlusion, 41 had M1 occlusion, 13 had M2 occlusion, 8 had BA occlusion, and 3 had PCA occlusion. Thus, 102 patients (56 men, 46 women; mean age, 75.2±11.2 years) were enrolled into the present study.

3.1. The time from symptom onset to treatment

The times from symptom onset to the initial MRI study and to treatment were 98.8±40.6 min and 141.0±32.3 min, respectively. The 102 patients were divided into 9 subgroups according to OTT: 13 in ≤100 min; 7 in 101–110 min; 8 in 111–120 min; 11 in 121–130 min; 6 in 131–140 min; 10 in 141–150 min; 11 in 151–160 min; 11 in 161–170 min; and 25 in 171–180 min. Table 1 shows the clinical characteristics of the 9 subgroups.

3.2. Early recanalization rate within 1 h after t-PA infusion

Follow-up MRA after t-PA infusion showed early recanalization in 42 (41.2%) patients (complete in 13 patients, partial in 29) within 1 h. κ statistics of agreements with the grade of early recanalization between two investigators was 0.88.

Regarding the site of occlusion, the early recanalization rate was 29.0% in ICA occlusion, 46.3% in M1 occlusion, 47.4% in M2 occlusion, 37.5% in BA occlusion, and 33.3% in PCA occlusion ($P=0.6021$). With respect to the OTT, the early recanalization rate was 53.8% in ≤100 min, 57.1% in 101–110 min, 50.0% in 111–120 min, 63.6% in 121–130 min, 33.3% in 131–140 min, 30.0% in 141–150 min, 36.4% in 151–160 min, 18.2% in 161–170 min, and 32.0% in 171–180 min (Table 2). The early recanalization rate and OTT were negatively correlated ($r=-0.767$, $P=0.0301$, Fig. 1), which indicated that early recanalization within 1 h after t-PA infusion was dependent on time from stroke onset to treatment.

Using ROC curve analysis, cut-off time of OTT that predicted patients with early recanalization was 130 min. Therefore, we divided the patients into two subgroups according to OTT of ≤ and >130 min. The early recanalization rate was higher in OTT of ≤130 min than >130 min (56.4% vs. 30.2%, $P=0.0086$). After adjusting the presence of age (>74), ICA occlusion, baseline NIHSS score (<10), and glucose (>150 mg/dl) as variables that are thought to be associated with no early occlusion, adjusted OR of OTT ≤130 min against OTT >130–180 min was 2.97 (95% CI 1.27–6.96, $P=0.012$) for early recanalization.

3.3. Cerebral hemorrhage on T2* 24 h after t-PA infusion

Three patients did not have follow-up MRI 24 h after t-PA infusion because of a severe stroke. Thus, ICH was observed in 37.4% of 99

Table 1
Patients' clinical characteristics.

		Time interval from stroke onset to t-PA administration (min)								
	Total	≤100	101–110	111–120	121–130	131–140	141–150	151–160	161–170	171–180
	No = 102	N = 13	N = 7	N = 8	N = 11	N = 6	N = 10	N = 11	N = 11	N = 25
Age (years)	75.2 ± 11.2	74.4 ± 9.8	76.7 ± 10.6	70.9 ± 10.1	73.4 ± 7.0	73.2 ± 7.1	80.4 ± 8.8	76.5 ± 12.6	75.7 ± 16.8	75.0 ± 12.5
Female	46(45.1%)	7(53.8%)	2(28.6%)	1(12.5%)	1(9.1%)	3(50.0%)	9(90.0%)	6(54.5%)	4(36.4%)	13(52.0%)
Time from symptom onset to treatment, min	141.0 ± 32.3	82.9 ± 18.4	107.7 ± 1.80	115.8 ± 4.1	125.5 ± 3.2	135.3 ± 2.6	147.6 ± 2.2	157.0 ± 2.8	165.1 ± 2.5	176.4 ± 3.1
Hypertension	65(63.7%)	6(46.2%)	6(85.7%)	6(75.0%)	6(54.5%)	3(50.0%)	7(70.0%)	7(63.6%)	7(63.6%)	17(68.0%)
Diabetes mellitus	17(16.7%)	4(30.8%)	2(28.6%)	1(12.5%)	0(0%)	1(16.7%)	0(0%)	1(9.1%)	2(18.2%)	6(24.0%)
Hyperlipidemia	23(22.5%)	5(38.5%)	1(14.3%)	3(37.5%)	3(27.3%)	1(16.7%)	2(20.0%)	0(0%)	2(18.2%)	6(24.0%)
Atrial fibrillation (AF)	61(59.8%)	8(61.5%)	5(71.4%)	4(50.0%)	3(27.3%)	3(50.0%)	7(70.0%)	8(72.7%)	9(81.8%)	14(56.0%)
NIHSS score										
Baseline (median, range)	17(3–32)	13(4–22)	21(11–26)	16(6–25)	16(5–20)	15.5(4–25)	19.0(8–29)	18(5–26)	15(6–32)	18(3–32)
24 h after t-PA infusion	12(0–40)	9(0–21)	8(1–20)	7.5(0–27)	6(0–24)	11.5(0.23)	12(4–29)	13(2–27)	15(0–31)	14(0–40)
7 days	10(0–40)	7(0–40)	7(1–15)	7.5(0–30)	4(0–20)	10(0–23)	10.5(2–29)	13(0–40)	16(0–31)	13(0–40)
Baseline DWI-ASPECTS[a] (median)	8(2–10)	8(3–10)	7(5–10)	7.5(4–10)	8.5(3–10)	8(5–10)	8.5(5–10)	7(3–10)	7(2–10)	7(3–10)
Systolic blood pressure (mm Hg)	154.8 ± 20.5	154.3 ± 15.4	144.7 ± 22.9	149.5 ± 17.4	166.1 ± 17.8	160.2 ± 18.0	152.0 ± 18.9	158.3 ± 21.2	149.8 ± 18.8	155.1 ± 25.3
Diastolic blood pressure (mm Hg)	83.6 ± 15.8	84.8 ± 13.4	76.6 ± 15.4	82.0 ± 8.3	88.9 ± 17.1	88.2 ± 10.6	83.5 ± 17.1	86.9 ± 13.1	83.7 ± 19.5	80.4 ± 18.6
Glucose (mg/dl)	146.0 ± 40.6	139.2 ± 32.0	138.9 ± 39.8	120.9 ± 18.8	145.0 ± 53.4	164.2 ± 33.4	137.0 ± 22.8	144.8 ± 29.2	151.3 ± 40.6	157.4 ± 52.4
Stroke type										
Cardioembolic stroke	62	7	4	6	3	4	8	8	9	13
Large artery diseases	7	0	0	1	3	1	0	0	1	1
Undetermined stroke	33	6	3	1	5	1	2	3	1	11
Occluded artery										
ICA	31	3	3	1	4	2	4	5	4	5
M1	41	5	2	5	4	3	2	5	6	9
M2	19	4	2	2	2	0	3	1	0	5
BA	8	0	0	0	1	1	1	0	0	5
PCA	3	1	0	0	0	0	0	0	1	1
Intracranial hemorrhage on T2[a] 24 h[b]	37/99(37.4%)	4(30.8%)	2(28.6%)	2(25.0%)	6(54.5%)	1(16.7%)	6(60%)	3/10(30.0%)	5(45.5%)	8/23(34.8)

[a] DWI ASPECTS, excluded 11 patients with BA and PCA occlusion.
[b] T2*, excluded 3 patients because no MRI study done due to severe stroke.

patients. Symptomatic ICH within 24 h after t-PA infusion was seen in one patient with a baseline NIHSS score of 7. OTT and ICH frequency were not correlated ($r = -0.100$, $P = 0.7773$).

3.4. Baseline and 7-day NIHSS scores

The median (range) of the baseline and 7-day NIHSS scores was 17 (3–32) and 10(0–40), respectively. Seven patients were excluded from the analysis of ΔNIHSS because they had mechanical thrombolysis after t-PA infusion. Three patients died within 7 days after t-PA infusion because of brain herniation, and the NIHSS scores of such patients were taken as 40. The median NIHSS score of 95 patients 7 days after t-PA infusion was 10(0–40). The median ΔNIHSS score between baseline and 7 days was 5(−29–26). The Spearman rank correlation coefficient was −0.205 ($P = 0.0484$). Therefore, OTT and ΔNIHSS were significantly negatively correlated, which indicated that neurological recovery within 7 days after t-PA infusion was dependent on time from stroke onset to treatment.

Dramatic improvement, good improvement, and worsening 7 days after t-PA infusion were observed in 38, 19, and 18 patients, respectively. Dramatic recovery was more frequent in patients with early recanalization than in those without (63.2% vs. 25.0%, $P = 0.0003$). Regarding OTT, the frequency of combined dramatic and good improvement was 66.7% in ≤100 min, 100% in 101–110 min in 7, 62.5% in 111–120 min, 60.0% in 121–130 min, 80.0% in 131–140 min, 62.5% in 141–150 min, 60.0% in 151–160 min, 40.0% in 161–170 min, and 48.0% in 171–180 min. The OTT and frequency of dramatic and good improvement were negatively correlated ($r = -0.773$, $P = 0.0288$).

3.5. mRS score at 3 months after t-PA therapy

21(20.6%) patients had favorable outcome, and 62(60.8%) patients had poor outcome. When excluded 15 patients with mRS >2 before t-PA infusion, and of 87 patients, 21(25.6%) had favorable outcome, and 44(53.7%) had poor outcome. The frequency of favorable outcome

Table 2
Early recanalization rate.

		Time interval from stroke onset to t-PA administration (min)								
	Total	≤100	101–110	111–120	121–130	131–140	141–150	151–160	161–170	171–180
	No = 102	N = 13	N = 7	N = 8	N = 11	N = 6	N = 10	N = 11	N = 11	N = 25
Early recanalization within 1 h	42(41.2%)	7(53.8%)	4(57.1%)	4(50.0%)	7(63.6%)	2(33.3%)	3(30.0%)	4(36.4%)	2(18.2%)	8(32.0%)
Partial	29	5	4	2	5	1	3	4	2	3
Complete	13	2	0	2	2	1	0	1	0	5

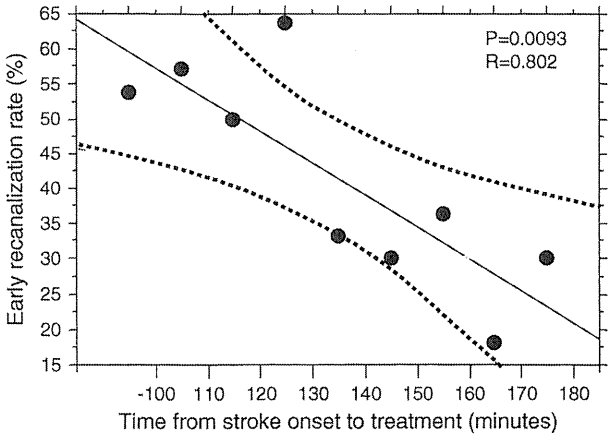

Fig. 1. Graph shows the correlation between time from stroke onset to t-PA administration and early recanalization rate within 60 min (95% confidence bands) after end of t-PA infusion.

was 46.2% in ≤100 min, 33.3% in 101–110 min, 42.9% in 111–120 min, 50.0% in 121–130 min, 20.0% in 131–140 min, 14.3% in 141–150 min, 33.3% in 151–160 min, 25.0% in 161–170 min, and 22.7% in 171–180 min. The frequency of favorable outcome was higher in OTT of ≤130 min than >130 min (44.4% vs. 23.5%, $P=0.0397$). On the other hand, the frequency of poor outcome was 46.2% in ≤100 min, 33.3% in 101–110 min, 57.1% in 111–120 min, 30.0% in 121–130 min, 60.0% in 131–140 min, 57.1% in 141–150 min, 55.6% in 151–160 min, 75.0% in 161–170 min, and 68.2% in 171–180 min. The frequency of poor outcome was lower in OTT of ≤130 min than >130 min (41.7% vs. 64.7%, $P=0.0333$).

4. Discussion

In the present study, early recanalization was dependent on time from stroke onset to IV-t-PA administration. Furthermore, the OTT and frequency of good recovery rate were negatively correlated and the frequency of favorable outcome was higher in OTT of ≤130 min than >130 min. Thus, earlier IV t-PA administration should be associated with early recanalization and better outcome.

In the present study, early recanalization rate was 41.2%. Rha et al. [19] reported that early recanalization rate of intravenous fibrinolytic therapy was 46.2% using meta-analysis. As a result, our results were in the range of their studies. Our study used a t-PA dosage of 0.6 mg/kg, which the Japanese government has approved, not the internationally approved 0.9 mg/kg dosage. Therefore, a t-PA dosage of 0.6 mg/kg might be adequate for Japanese.

Early arterial recanalization has been recognized as a marker of good outcome after t-PA infusion [20,21]. In particular, Strbian et al. [20] mentioned that ultraearly thrombolysis was associated with better outcome in patients with moderate or severe symptoms. Marzighi et al. [22] also reported that in stroke patients treated with a combined intravenous–endovascular approach, a shorter time from symptom onset to recanalization was associated with better clinical outcome. On the other hand, von Kummer et al. [23] mentioned that even if delayed, arterial recanalization might improve clinical outcome in a subgroup of patients with MCA occlusion. Therefore, the occurrence of early recanalization is essential for patient outcome, but, earlier recanalization should be more important.

Marler et al. [12] analyzed the NINDS rt-PA stroke study and reported that patients treated earlier with rt-PA had a better outcome than patients treated later. Our results provide an explanation for this, because patients treated early with t-PA more frequently had earlier recanalization of the occluded artery than those treated later. Clot dissolution depends on clot size, site of occlusion, clot composition, surface area of clot exposed to blood flow, and penetration of t-PA into the clot structure [24]. Furthermore, thrombolysis may be more effective for fresh clots than for old thrombi. Therefore, we believe that even if patients were treated with t-PA within 3 h, patients treated earlier more frequently had early recanalization than those treated later. The results of the present study support Marler et al.'s results that early treatment was associated with better outcome.

Off course, all patients who had early recanalization did not always have favorable outcome. We reported that large ischemic lesions on DWI before IV t-PA thrombolysis was associated with a poor outcome [25]. Even if early recanalization after t-PA infusion occurred in such patients, the ischemic damage was so severe that clinical recovery was not likely. Furthermore, poor outcomes are associated with older age, atrial fibrillation, high acute blood pressure, neurological severity, hyperglycemia, and internal carotid artery (ICA) occlusion [1,16,20,21,26–28].

Marler et al. [12] reported that ICH after t-PA therapy was not more frequent in patients treated within 90 min than in those treated later, and OTT had no effect on ICH. In the present study, there was no relation between time from stroke onset to t-PA infusion and ICH frequency, which was compatible with Marler's results. Recently, Singer et al. [29] reported that a larger ischemic lesion before t-PA infusion was associated with symptomatic ICH, and that DWI-ASPECTS could predict symptomatic ICH. The SIST-MOST investigators reported that systolic blood pressure, atrial fibrillation, and weight were predictors of symptomatic ICH [30]. Within 3 h after stroke onset, ICH should not be associated with OTT.

Recently, the ECASSIII randomized trial of IV t-PA demonstrated that a time window of between 3 and 4.5 h after the onset of symptoms significantly improved clinical outcome in patients with acute ischemic stroke [2]. t-PA group more frequently had a favorable outcome than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; $P=0.04$). Therefore, the effect size in ECASS-III was approximately 7%. According to our results, the assumed rate of early recanalization at 4.5 h from stroke onset to treatment was less than approximately 10%. This rate may fit well with the 10% recanalization rate at 4.5 h in our study.

In the present study, MRA rather than TCD was used to evaluate the presence of recanalization of occluded arteries, because several cases of elderly female and/or Asian patients with an insufficient temporal bone window have been described [31]. Furthermore, there may be a difference between MRA and TCD in the ability to identify the presence of recanalization. MRA can identify the presence of ICA, M1, and M2 occlusion. However, TCD cannot always diagnose the presence of M2 occlusion, while MRA can accurately detect occluded M2 branches. Therefore, MRA should be more sensitive than TCD for the assessment of M2 occlusion and recanalization of M2 occlusion.

The present study had several limitations. MRA is somewhat inaccurate for detection of vessel occlusion or stenosis [32]. Secondly, MRI cannot be performed in patients who have had artificial metallic materials, such as pacemakers and metal clips, implanted. In fact, two such patients were excluded from the present study.

In conclusion, early recanalization depended on time from stroke onset to IV-t-PA administration. Good improvement at 7 days after t-PA infusion was more frequent in patients treated earlier than in those treated later. Thus, t-PA should be given to acute stroke patients as soon as possible.

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