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Clinical commentary

Early partial recanalization after intravenous thrombolysis leads to prediction of favorable outcome in cases of acute ischemic stroke with major vessel occlusion

Jun Young Chang [a], Hyun Park [b], Se Young Jang [c], Seunguk Jung [a], Hee-Joon Bae [d], O-Ki Kwon [e], Moon-Ku Han [d,*]

[a] Department of Neurology, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea
[b] Department of Neurosurgery, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea
[c] Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, Republic of Korea
[d] Department of Neurology, Seoul National University Bun-Dang Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
[e] Department of Neurosurgery, Seoul National University Bun-Dang Hospital, Seongnam, Republic of Korea

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ABSTRACT

We investigated the association between early recanalization degree after intravenous thrombolysis (IVT), occurrence of hemorrhagic transformation, and functional outcome. We also evaluated whether recombinant tissue plasminogen activator (rTPA) dosing error could influence the outcome. Patients with ischemic stroke with major vessel occlusion (n = 256) who underwent IVT were included. Recanalization status (no recanalization, partial recanalization, and complete recanalization) was confirmed by subsequent magnetic resonance or conventional angiography. Association between early recanalization degree and favorable outcome (modified Rankin Scale score ≤2) was evaluated using logistic regression analysis. Early partial recanalization was achieved in 33 (12.9%), and complete recanalization in 7 (2.7%) patients. Patients with the highest quintile of rTPA dosage achieved complete recanalization more frequently than the lower four quintiles (8.0% vs 2.0%, P = 0.03). Hemorrhagic transformation tended to occur more frequently in patients with complete recanalization as compared with patients with partial recanalization (57.1% vs 21.2%, P = 0.15). The proportion of favorable outcome was significantly lower in patients with the highest quintile of rTPA dosage used as compared with the patients with lower four quintiles (40.8%, 57.0%, P = 0.04). In multivariable analysis, partial recanalization was significantly associated with favorable outcome (adjusted odds ratio, 3.15; 95% CI, 1.06–9.35), but complete recanalization was not. Early partial recanalization after IVT may be an indicator of favorable outcome with low occurrence of any hemorrhagic transformation.

1. Introduction

The goal of thrombolytic therapy is to achieve recanalization of occluded cerebral vessels as early as possible. Introduction of mechanical thrombectomy with stent retrievers augments recanalization rate. However, there is still a discrepancy between successful recanalization and good outcome, with 18%–47.2% of patients not gaining functional independence after revascularization [1]. Various factors that include old age, initial severity, poor collateral circulation, nonexistent or minimal salvageable tissue, and proximal occlusion impede clinical improvement after recanalization [2–4]. Reperfusion induced intracerebral hemorrhage or cerebral edema could also exacerbate neurological status.

Early recanalization within 24 h after intravenous thrombolysis (IVT) is important to achieve favorable outcome after acute ischemic stroke [5]. However, minimizing reperfusion injury to prevent reperfusion induced hemorrhagic transformation, cerebral edema, or postischemic hyperperfusion after successful revascularization is also critical [6]. Conditioned blood reperfusion, brain cooling, and gradual opening of the occluded cerebral artery may mitigate overproduction of reactive oxygen species and inflammatory mediators, and subsequently reduce cerebral edema formation, blood-brain barrier breakdown, and final infarct volume [4,7].

The aim of this study was to evaluate the association between degree of early recanalization right after IVT and clinical outcome.

* Corresponding author at: Department of Neurology, Seoul National University Bun-Dang Hospital, Seoul National University College of Medicine, 82 Gumiro 173, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, South Korea.
E-mail address: mkhan@snu.ac.kr (M.-K. Han).

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We assessed whether the degree of recanalization is associated with the occurrence of hemorrhagic transformation and favorable functional outcome at 3 months. We also evaluated whether recombinant tissue plasminogen activator (rTPA) dosing error could have an impact on degree of early recanalization, hemorrhagic risk, and clinical outcome.

2. Methods

We reviewed the records of acute ischemic stroke patients with major vessel occlusion who underwent IVT in our institute between January 1, 2009 and December 31, 2013 from the single hospital-based stroke registry. Critical pathway was applied for patients suspected of acute stroke who came to the emergency room (ER) within 12 h from symptom onset. Brain computed tomography (CT), CT angiography, and perfusion CT were performed first on consideration of the rapid intravenous administration of rTPA if patients arrived within 4 h from symptom onset. Patients who arrived beyond 4 h from symptom onset were evaluated with a magnetic resonance imaging (MRI) stroke protocol consisting of diffusion weighted image (DWI), apparent diffusion coefficient (ADC) maps, T2-weighted, fluid-attenuated inversion recovery, and gradient-echo images in the axial plane, contrast enhanced T1-weighted, time of flight angiography for intracranial and extracranial arteries, and perfusion weighted image (PWI). Patients with acute ischemic stroke within 4.5 h of symptom onset were considered suitable candidates for IVT. Patients with malignant profile (early ischemic change in more than one-third of middle cerebral artery territory), Alberta Stroke Program Early CT score (ASPECTS) <6, or >100 cc on initial brain CT were excluded. IVT was performed according to the guidelines of the National Institute of Neurological Disorders and Stroke rTPA Stroke Study and the Clinical Research Center for Stroke. According to the results of Japan Alteplase Clinical Trial II (J-ACT II) and Japan post-marketing Alteplase Registration Study (J-MARS), we used a reduced dose of rTPA (0.6 mg/kg, with 15% as a bolus injection and the remnant infused over a period of 30 minutes) [8,9]. Owing to urgent rTPA administration and insufficient weight measuring equipment for bedridden patients in the ER, body weight estimates from the patients, family members, or attending physician was used. Actual administered dosage of rTPA (in mg/kg) was calculated by dividing total rTPA dose given by actual body weight measured with in-bed scale right after admission to the stroke unit. Demographics (age, sex, body weight) and baseline characteristics of the patients including vascular risk factors (history of stroke, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, and coronary artery disease), initial laboratory findings that included total cholesterol, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), glucose, hemoglobin A1c (HbA1c), and platelet count, and initial systolic and diastolic blood pressure, dosage of rTPA used, occluded vessel, stroke mechanism, initial National Institutes of Health Stroke Score (NIHSS), time from symptom onset to IVT, recanalization status after IVT, and clinical outcome (modified Rankin Scale (mRS) score at 3 months, occurrence of any or symptomatic intracranial hemorrhage) were retrospectively reviewed.

Major vessel occlusion included middle cerebral arteries (M1, M2), posterior cerebral arteries (P1, P2), anterior cerebral arteries (A1, A2), internal cerebral artery, basilar artery, and vertebral artery. Recanalization status was confirmed by subsequent MR angiography (MRA) or conventional angiography in case of performing CT angiography first, and by conventional angiography in case of performing MRA first. Partial recanalization (PR) was defined as modified Mori grade 2 (partial recanalization in <50% of the branches in the occluded arterial territory) on MRA, [9] or thrombolysis in cerebral infarction (TICI) grade 2 on conventional angiography. Complete recanalization (CR) was defined as modified Mori grade 3 on MRA, or TICI grade 3 on conventional angiography.

Symptomatic intracranial hemorrhage (SICH) was defined as detection of any blood on CT accompanied by neurological deterioration $\geq$4 of NIHSS within 36 h after treatment [10]. Any ICH included detection of any blood on CT $\geq$ hemorrhagic infarction type 1 (HI1) within 36 h after treatment [11].

Mechanism of occlusion was determined based on consensus of several neurologists who attended a regular registration meeting according to the MRI-based Algorithm for Acute ischemic stroke Subtype Classification (MAGIC) [12]. Functional outcome was evaluated by a neurologist at the outpatient clinic or, if unavailable, determined through structured telephone interview by a trained nurse after 3 months. Favorable outcome was defined as mRS score $\leq$2.

Seoul National University Bundang Hospital Institutional Review Board approved the retrospective study.

2.1. Statistical analyses

Baseline characteristics were summarized and compared according to functional outcome. Chi-square test or Fisher's exact test was used to analyze categorical variables, while the independent *t* test or Mann-Whitney *U* test was used for continuous variables. The primary outcome was favorable neurological outcome at 3 months and the primary predictor was degree of early recanalization. Binary logistic regression analysis was performed to estimate odds ratio (OR) and 95% confidence intervals (95% CI) for the association between recanalization degree and functional outcome (unadjusted, adjusted for age, sex, and initial NIHSS; and adjusted for age, sex, initial NIHSS, history of smoking, history of dyslipidemia, occurrence of any intracranial hemorrhage, rTPA dosage administrated, TG, glucose, HbA1c, and diastolic blood pressure). Goodness of fit was evaluated using Hosmer-Lemeshow test. The predictive logistic model was internally validated by bootstrap simulations. These analyses were performed using Stata version 13.0 (StataCorp., Austin, TX, USA). All tests were 2-sided, and P-values of <0.05 were considered significant.

3. Results

Among 3692 consecutive patients with acute ischemic stroke who visited the ER between January 1, 2009 and December 31, 2013, 405 (11.0%) patients underwent IVT. Major vessel occlusion was documented in 274 (67.7%) of these patients. Eighteen patients with premorbid mRS $\geq$3 were excluded and 256 patients were eligible for the final analysis (Supplementary 1). Vessel occlusion site was as follows in order of frequency; M1 (87, 34.0%), M2 (47, 18.4%), distal ICA (47, 18.4%), proximal ICA (37, 14.5%), basilar (20, 7.8%), vertebral (5, 2.0%), P2 (6, 2.3%), P1 (4, 1.6%), and A2 (3, 1.2%). Recanalization status was confirmed by subsequent MRA in 35 (13.7%) and by, conventional angiography in 221 (86.3%). Median time from IVT to MRA was 35.0 min (range, 23.0–47.0), and from IVT to conventional angiography was 66.0 min (range, 45.0–82.0). Baseline characteristics and variables according to clinical outcome are listed in Table 1. Median age was 72.0 years (range, 60.5–79.0 years). Male comprised 58.6% of the patients. The mean NIHSS was 14.1 ± 7.2. Median time from symptom onset to IVT was 157.9 min (range, 78.5–173.0). Recanalization was achieved in 40 (15.6%) of the 256 patients during or right after intravenous thrombolysis. PR was achieved in 33 (12.9%), and CR in 7 (2.7%) patients. Subsequent endovascular treatment was performed in 18 of 33 patients with PR (55%). Any ICH was observed in 65 (25.4%) patients and SICH occurred in 22 (8.6%) patients.

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