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The clinical value of antiplatelet therapy for patients with hemorrhage after thrombolysis based on susceptibility-weighted imaging: A prospective pilot study

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ABSTRACT

Purpose: To evaluate treatment decision-making based on susceptibility-weighted imaging (SWI) in patients with hemorrhage after thrombolysis.
Materials and methods: One hundred and forty-six patients without intracranial hemorrhage on CT after receiving recombinant tissue plasminogen activator (rt-PA) were allocated to two groups: antiplatelets ($n = 72$), who received antiplatelet therapy 24 h after rt-PA for 10 days; and non-antiplatelets ($n = 74$), who received no antiplatelet therapy. Twenty-two patients with SWI-detected microbleeds (MBs) or hemorrhagic transformation (HT) in the antiplatelets group (Group A) and 28 with MB or HT in the non-antiplatelets group (Group B) were included in this study.
Results: Sixteen patients had MB and six HT in Group A; 18 had MB, six HT, and four parenchymal hemorrhage (PH) in Group B. National Institutes of Health Stroke Scale (NIHSS) scores at 7 and 14 days and the Modified Rankin Scale (mRS) at 90 days post-rt-PA were significantly lower in Group B than in Group A, duration of hospitalization was significantly shorter, and the favorable outcome rate was higher at 90 days ($P < 0.05$). There were no other significant differences. SWI evaluation at 14 days revealed eight patients with MB, 11 HT, and three PH in Group A; in Group B, 16 had MB, five HT, and one PH, with resolution of hemorrhage in six patients.
Conclusions: Treatment decision-making based on SWI in acute stroke after thrombolysis was validated by the significantly reduced NIHSS score after 7/14 days, improved outcome, and reduced mRS in hemorrhage patients without antiplatelet therapy.

1. Introduction

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) and secondary anticoagulation with heparin to prevent rethrombosis in acute stroke patients has been shown to be beneficial in large randomized trials [1], but the major complication of this therapy is secondary postischemic symptomatic intracranial hemorrhage (SICH) [2], which can be devastating. Therefore, it is necessary to detect microbleeds (MBs) or hemorrhagic transformation (HT) early and accurately, and to institute rapid treatment decision-making according to neuroimaging findings to prevent development of a hemorrhage-prone state and improve neurologic recovery [3–6].

Recently, susceptibility-weighted imaging (SWI) has become a sensitive marker for the accurate detection of MB or HT after ischemic stroke [5,7–10], but the clinical implications of protocols that use SWI as a pretreatment planning tool are unclear. To evaluate treatment decision-making based on SWI in hemorrhage patients after thrombolysis, we compared the efficacy of treatment in patients with SWI-detected MB or HT after thrombolysis with and without antiplatelet therapy.

2. Materials and methods

2.1. Study design

This prospective clinical study was conducted between January, 2007 and September, 2009. The institutional review board approved the study and patient (or legal representative) consent was obtained before study enrolment.

Abbreviations: rt-PA, recombinant tissue plasminogen activator; SWI, susceptibility-weighted imaging; DWI, diffusion-weighted imaging; MB, microbleeds; SICH, symptomatic intracranial hemorrhage; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale.

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Patients were eligible for thrombolysis if they met the following criteria: (1) documented clinical signs and symptoms of acute circulatory stroke; (2) National Institutes of Health Stroke Scale (NIHSS) score [11] ranging from 4 to 22 at baseline; (3) age 18–80 years; (4) thrombolytic therapy administered within 6 h of symptom onset; and (5) absence of intracranial hemorrhage confirmed by computed tomography (CT) before and within 24 h of thrombolysis.

Patients were excluded from thrombolysis if any of the following criteria were present: (1) intracranial hemorrhage, cerebral stroke of any etiology, or myocardial infarction in the past 3 months; (2) history of alimentary canal or urinary system hemorrhage or trauma in the last 3 weeks; (3) current anticoagulation therapy; (4) personal or family history of hemorrhagic tendency or hemorrhagic disease; or (5) history of circulatory failure or uncontrolled hypertension, severe cardiac, renal or hepatic inadequacy, severe diabetes, or current pregnancy. Patients were also excluded for the following reasons: (1) lacunar infarctions on MRI; (2) MRI follow-up or clinical scoring was refused; (3) MRI was incomplete because of technical reasons or the subject's inability to cooperate; and (4) an apparent diffusion-weighted imaging (DWI) lesion exceeded 70% of the territory of the ipsilateral hemisphere.

Two hundred and four consecutive patients with acute stroke were screened by MRI within 6 h after symptom onset, before thrombolysis. MRI revealed no infarction in 21 patients, lacunar infarction in 19 patients, hemorrhage (MB = 12, HT = 2) in 14 patients, and a huge acute ischemic lesion in four patients. All of these patients ($n = 58$) were excluded from the study due to ineligibility for rt-PA thrombolytic therapy. As a result, 146 patients with acute ischemic stroke who were eligible for intravenous rt-PA thrombolysis were enrolled in the study. These comprised 96 men and 50 women with a mean age of 65.77 ± 8.91 years (range: 49–80 years). The standard dose for intravenous rt-PA therapy was 0.9 mg/kg body weight, with a maximal dose of 90 mg. Ten percent of the total dose (0.9 mg/kg) was injected as an intravenous bolus for 1 min; the remainder was given by continuous intravenous infusion over the next 59 min.

After thrombolysis, no patient exhibited SICH on CT within 24 h and all were randomly allocated to two groups: antiplatelets ($n = 72$) or non-antiplatelets ($n = 74$). SWI-detected MB or HT was present in 22 patients in the antiplatelets group and in 28 patients in the non-antiplatelets group. Patients in the antiplatelets group received antiplatelet therapy 24 h after rt-PA for 10 days. Antiplatelet therapy was stopped in those who developed SICH or exhibited an increase in NIHSSS score of $\geq$4 points. Patients in the non-antiplatelets group did not receive antiplatelet therapy. To evaluate treatment decision-making based on SWI in hemorrhage patients after thrombolysis, we included only patients with SWI-detected MB or HT in the analysis.

2.2. MRI protocol

All sequences were performed using a GE 1.5T MRI scanner with an eight-channel head coil and parallel acquisition technique. The protocol comprised DWI, axial fast spin-echo with T1- and T2-weighted imaging, three-dimensional time-of-flight magnetic resonance angiography, axial flow-attenuated inversion recovery, and perfusion-weighted imaging (PWI). Before the PWI sequence, SWI was performed. The SWI parameters were: repetition time/echo time = 40/26 ms; flip angle = 20°; field of view = 24 cm; matrix = 512×256; and section thickness = 2 mm, with 32 slices. The acquisition time for SWI was 3 min 49 s and the overall time was 12–15 min. All images were acquired in the same axial plane. Subsequently, the SWI sequences were reconstructed using the minimum intensity projection technique to obtain images with section number, thickness, and position similar to those of the T1-weighted, T2-weighted, and DWI sequences.

Baseline DWI lesion volumes were measured by two of the authors (Y.H.L. and H.R.Q., with 8 and 15 years of experience, respectively, in neuroradiology) using the software available at the workstation (EWS 2.5.3.0, Philips). Areas of hyperintensity on DWI were traced manually on each slice, summed, and multiplied by the slice thickness and interslice gap to obtain the DWI lesion volume [12].

2.3. Definition of hemorrhage

MBs were defined as punctate, homogeneous, rounded, hypointense lesions of size <0.5 cm on SWI sequences [6]. HT was defined as petechial or confluent hemorrhage within the ischemic lesion according to the standard definition [13]. Parenchymal hemorrhage (PH) was defined as blood clots in the infarcted area with at least a slight space-occupying effect. SICH was defined as any sign of hemorrhage on follow-up imaging associated with clinical deterioration of $\geq$4 points on the NIHSS within 36 h [14]. Interpretation was performed independently by two experienced neuroradiologists blinded to the clinical data. In cases of discrepancy between the two raters, the scans were reviewed simultaneously by both and a consensus was achieved.

2.4. Follow-up imaging protocol

Follow-up protocols included clinical and multiparametric MRI evaluation as well as brain CT performed by one of two authors (Y.D.L. or M.H.L., with 5 and 15 years of experience, respectively, in neurointerventional radiology). Clinical follow-up conducted 90 days after thrombolysis recorded changes from the preliminary clinical presentation and thrombolysis- or disease-associated adverse events (defined as ischemic stroke, intracranial hemorrhage, neurologic deficient, or death). MRI and CT were performed 6 h, 24 h, 7 days, and 14 days after thrombolysis. Whenever neurological worsening (NIHSSS increase $\geq$4 points) occurred, CT was performed immediately to exclude SICH.

2.5. Clinical assessment

We assessed the patients' clinical status before administration of rt-PA and 6 h, 24 h, 48 h, 7 days, and 14 days after thrombolysis by means of the NIHSS [11], which was assessed by two experienced stroke neuroradiologists (M.H.L. and J.G.Z., with 15 and 8 years of experience, respectively, in neurointerventional radiology). When there was disagreement, a consensus was reached. The Modified Rankin Scale (mRS) [15] was used together with a semi-structured interview conducted either by telephone or in person to assess the clinical outcome at 30 and 90 days after thrombolysis. All outcome variables (favorable outcome, independent outcome, hemorrhage, or death) were assessed independently by physicians unaware of the patients' initial stroke severity, time to treatment, and imaging modality. A favorable outcome at day 90 was defined as a mRS score of 1; an independent outcome was a mRS score of 2.

2.6. Statistical analysis

Data are presented as the mean $\pm$ standard deviation. Group comparisons were made using the Mann–Whitney U test for continuous variables and the Fisher exact test for categorical variables. The significance of pain relief over time was determined using the Kaplan–Meier method and the log rank test was used to evaluate group differences. A two-sided P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS package, version 13.0 (SPSS, Chicago, Illinois, USA).