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Subacute lesion volume as a potential prognostic biomarker for acute ischemic stroke after intravenous thrombolysis☆,☆☆

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ABSTRACT

Background: The aim of this study was to identify whether subacute diffusion-weighted imaging (DWI) lesion volume could predict long-term outcome in patients who had undergone intravenous thrombolysis.
Method: Patients underwent DWI at baseline and 7 days after thrombolysis. Outcomes included complete independence (modified Rankin scale [mRS] score 0 to 1), unfavorable outcome (mRS score 4 to 6) at 90 days, and mortality within 90 days. Multivariate logistic regression analysis was used to identify outcome predictors.
Results: Of 164 patients, 72 patients (43%) achieved complete independence. Poor outcomes were observed in 45 patients (27%) with an unfavorable outcome and 10 patients (6%) who died. Subacute DWI lesion volume was 3.4 mL (interquartile range, 1.1–11.6) in patients with complete independence, 90.1 mL (23.8–180.2) in patients with unfavorable outcome and 155.5 mL (78.4–377.5) in patients who died. In multivariate logistic regression analysis, subacute DWI lesion volume was an independent predictor of complete independence (odds ratio [OR], 0.939; 95% confidence interval [CI], 0.914–0.965; $p < 0.001$), unfavorable outcome (OR, 1.023; 95% CI, 1.014–1.033; $p < 0.001$), and mortality (OR, 1.016; 95% CI, 1.005–1.028; $p = 0.005$).
Conclusion: Subacute DWI lesion volume is a critical determinant of 90-day functional outcome and mortality after thrombolysis.

1. Introduction

Approximately half of patients who receive intravenous recombinant tissue-type plasminogen activator (IV rt-PA) have a favorable outcome (modified Rankin scale [mRS] score 0–1) [1]. Several predictive factors (age, stroke severity, onset-to-treatment time, blood glucose level, cerebral artery occlusion, and ischemic lesion) influence final functional outcomes after IV rt-PA [2–4].

To avoid futile treatment, evaluation of predictive factors for outcome could be crucial before IV rt-PA. Diffusion-weighted imaging (DWI) before IV rt-PA could predict outcome [5–7]. However, patients who have small infarct volume before IV rt-PA do not always have good outcomes, because a DWI hyperintense lesion could change dynamically during the first few days [8,9]. Stroke location might also be associated with stroke outcomes rather than initial infarct volume [10]. In this study, we focused on subacute DWI lesion volume. The lesion is considered as a "true" final infarct volume at 30 days [11] and 90 days [12], because the outcome was evaluated at the same time in stroke patients treated with IV rt-PA. Gaudinski et al. reported that a volume change between day 30 and day 90 was insignificant. Therefore, they concluded that day 30 is a reliable time point for measurement of final infarct volume [13]. It would be beneficial to predict the prognosis before the patient's discharge from the hospital. Subacute volume assessed during the first week could accurately predict chronic volume at 30 days and clinical outcome [14]. The aim of this study was to confirm that the lesion volume provided by DWI in the subacute phase could predict the outcome at 90 days in acute stroke patients who had undergone IV rt-PA therapy.

2. Methods

2.1. Patients

Between April 2010 and December 2015, consecutive patients admitted to our hospital with acute ischemic stroke in anterior and

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posterior circulation within 4.5 h of onset were studied. Their charts were retrospectively reviewed, and patients who had undergone IV rt-PA therapy were included. We excluded patients whose mRS score was 3 or higher before onset, and who had a contraindication to MR imaging. An experienced stroke neurologist (J. H), who was blind to the findings of MR imaging, rated clinical outcomes according to the mRS score at 90 days. Clinical outcomes were dichotomized as complete independence (mRS score 0–1 vs. 2–6), unfavorable outcome (mRS score 4–6 vs. 0–3), and death (mRS score 6 vs. 0–5). The study was approved by the institutional review board at the Nagasaki University Hospital (Nagasaki, Japan).

2.2. MR imaging protocol

Brain MR imaging was routinely performed to identify IV rt-PA candidates in our hospital. DWI at baseline and day 7 (±2) were assessed by an experienced neuroradiologist (M.M) blinded to patients' clinical status. Brain MR imaging studies were performed using a commercially available echo planar instrument on a 1.5-T MR unit (Signa HDxt; GE Healthcare, Milwaukee, WI). The neuroimaging protocol for this study included the T2-weighted fluid-attenuation inversion recovery sequence (repetition time [TR]/echo time [TE], 8000 ms/110 ms; inversion time, 2000 ms; field-of-view [FOV], 22 cm; acquisition matrix, 256 × 192; and section thickness, 5 mm with a 1-mm intersection gap), DWI sequence (TR/TE, 10,000 ms/82 ms; b values, 0 and 1000 s/mm^2; FOV, 27 cm; acquisition matrix, 128 × 192 matrix; and 5 mm with a 1-mm intersection gap), 3D time-of-flight MR angiography covering the circle of Willis (TR/TE, 28 ms/3.3 ms; 20° flip angle, FOV, 19 cm; acquisition matrix, 192 × 320 matrix; and 1.4-mm slice thickness with zero-filled interpolation), and 3D multi-echo gradient echo T2 star-weighted MR angiography (TR/effective TE, 63.8 ms/49.8 ms; 15° flip angle; field-of-view, 22 cm; acquisition matrix, 192 × 384 matrix, and 3-mm slice thickness).

2.3. Radiological measurements

DWI lesion volume was determined by calculating the sum of the infarct area on each slice and summed individual slice thicknesses of the entire outlined area. The abnormal lesions on DWI were visually defined by comparison with the contralateral non-affected hemisphere. The window level and window width were chosen to obtain the best contrast between the lesion and the surrounding normal tissues. The level of occlusion was defined based on initial MR angiography. Considerable hemorrhagic transformation was defined as parenchymal hematoma type 1 or 2 [15].

2.4. Thrombolysis protocol

Each patient received IV rt-PA (0.6 mg/kg) with 10% given as a bolus within 4.5 h of stroke onset followed by a continuous IV infusion of the remainder in 1 h. Furthermore, if a clinical-DWI mismatch (clinical deficit out of proportion to DWI lesion, approximately < 70 mL volume core infarct by visual inspection) with concomitant large-vessel occlusion (intracranial internal carotid artery, middle cerebral artery M1, and basilar artery) on MR angiography was found, endovascular recanalization therapy was performed using a MERCI device (Concentric Medical Inc., Fremont, CA), a Penumbra Aspiration System (Penumbra Inc., Alameda, CA), and/or stent-based mechanical thrombectomy (Solitaire: Covidien, Irvine, CA and Trevo: Stryker, Kalamazoo, MI).

2.5. Clinical assessment

The National Institutes of Health Stroke Scale (NIHSS) score was used to assess stroke severity. All patients underwent blood tests on admission. The main parameters were brain natriuretic peptide (BNP), C-reactive protein (CRP), glucose, D-dimer, serum albumin and estimated glomerular filtration rate (eGFR). Stroke subtypes were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

2.6. Analysis

Clinical and imaging baseline parameters were compared between patients with good and poor outcomes according to the clinical outcome criteria. Numerical or continuous variables are presented as medians (interquartile range [IQR]) using the Mann-Whitney *U* test. Categorical variables were analyzed by the chi-squared test or Fisher's exact test. To identify independent predictors of the clinical outcomes, multivariate logistic regression analysis with the backward elimination method was performed. Variables that were significantly associated with the clinical outcomes on univariate analyses ($p < 0.1$) were included in the multivariate model. To elucidate the cut-off value of subacute DWI lesion volume for predicting clinical outcomes, the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was evaluated for each model. Sensitivity and specificity using the cut-off value to predict clinical outcomes were also calculated. Results were considered significant when the p value was <0.05. All analyses were performed using IBM SPSS software for Windows, version 18 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 176 patients underwent IV rt-PA therapy during the study period. Six patients with pacemaker implantation and six patients with mRS score 3 or higher before onset were excluded. Of 164 enrolled patients, 87 were male (53%), with a median age of 76 years (IQR 68–82 years), a median NIHSS score of 12 (IQR 7–18), and median time from stroke onset to IV rt-PA therapy of 123 min. (IQR 103–173 min). The median time from onset to baseline MRI was 90 min (IQR 72–135 min), and the median time between initial and subacute MRI was 7 days (IQR 5–8 days). The median DWI lesion volumes at baseline and in the subacute stage were 4.21 mL (IQR 1.31–17.48 mL) and 12.83 mL (IQR 2.82–56.13 mL), respectively. Stroke subtypes included cardioembolism (n = 93, 57%), large artery atherosclerosis (n = 24, 15%), small vessel occlusion (n = 15, 9%), stroke of other determined etiology (n = 2, 1%) and stroke of undetermined etiology (n = 30, 18%). Overall, 72 patients (43%) achieved complete independence (mRS score 0–1) at 90 days, 45 patients (27%) had an unfavorable outcome (mRS score 4–6), and 10 patients (6%) had died by 90 days.

The results of the univariate analyses are shown in Table 1. Variables related to poor outcome at 90 days were older age, atrial fibrillation, higher initial NIHSS score, higher BNP level and D-dimer level, lower serum albumin level, internal carotid artery occlusion, larger baseline and subacute DWI lesion volumes, and parenchymal hematoma. Baseline DWI lesion volume was associated with complete independence ($p = 0.001$) but not with unfavorable outcome ($p = 0.121$) and death ($p = 0.052$). In contrast, subacute DWI lesion volume was associated with all outcomes (complete independence: median, 3.4 [IQR 1.1–11.6 mL] vs. 42.2 mL [IQR 12.1–120.7 mL]; $p < 0.001$, unfavorable outcome: median, 90.1 [IQR 23.8–180.2 mL] vs. 7.6 mL [IQR 1.8–25.5 mL]; $p < 0.001$, and death: median, 155.5 [IQR 78.4–377.5 mL] vs. 12.2 mL [IQR 2.7–46.3 mL]; $p = 0.001$).

Multivariate logistic regression analysis showed that age (odds ratio [OR], 0.937; 95% confidence interval [CI], 0.895–0.980; $p = 0.004$) and subacute DWI lesion volume (OR, 0.939; 95% CI, 0.914–0.965; $p < 0.001$) were independent predictors of complete independence at 90 days. Independent predictors of unfavorable outcome were age (OR, 1.081; 95% CI, 1.026–1.139; $p = 0.004$), prior antiplatelet drug use (OR, 3.015; 95% CI, 1.123–8.091; $p = 0.028$) and subacute DWI lesion volume (OR, 1.023; 95% CI, 1.014–1.033; $p < 0.001$), and those of death were prior antiplatelet drug use (OR, 9.541; 95% CI, 1.401–64.988; $p = 0.021$), and subacute DWI lesion volume (OR, 1.016; 95%