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Early infarct growth predicts long-term clinical outcome in ischemic stroke

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ABSTRACT

Background: Ischemic lesions dynamically evolve during the acute phase of stroke. Although the ischemic lesion volume has been considered as a predictor of clinical outcome, it is still controversial whether early changes in ischemic lesion have prognostic information in addition to clinical variables. We hypothesized that early infarct growth on diffusion-weighted imaging (DWI) might be independently associated with long-term outcome in acute ischemic stroke patients.

Methods: This was a prospective study for acute ischemic stroke patients admitted to the Stroke Unit of Asan Medical Center. The patients underwent DWI at baseline (within 24 h) and subsequently at 5 days after stroke onset. Early infarct growth was defined as the absolute difference between follow-up and baseline infarct volumes. Poor outcome was a modified Rankin Scale (mRS) at 3 months of 2–6 or 3–6. The association between infarct growth on DWI and clinical outcome was explored using multivariate analysis adjusting for demographics, risk factors for stroke, and other clinical variables. The cut-off values of early infarct growth predicting long-term outcomes were estimated using receiver operating characteristic analysis.

Results: Of 409 patients enrolled, 345 (84.4%) showed any infarct growth (median, 0.63 cm^3; interquartile range [IQR], 0.11–6.33 cm^3; mean ± standard deviation, 9.55 ± 25.54 cm^3). At the 3-month follow-up, the good outcomes were observed in 217 patients (53.1%) for mRS 0–1 and 303 patients (74.1%) for mRS 0–2. The larger infarct growth was associated with poor clinical outcome (for mRS 2–6, 0.29 cm^3 [IQR 0.04–2.19] vs. 2.16 cm^3 [IQR 0.26–17.68], $p < 0.001$; and for mRS 3–6, 0.39 cm^3 [IQR 0.05–3.25] vs. 7.36 cm^3 [IQR 0.57–26.48], $p < 0.001$). After adjusting age, diabetes, baseline National Institutes of Health Stroke Scale, and baseline infarct volume by multivariate logistic regression analysis, infarct growth was an independent predictor of poor clinical outcomes (for mRS 2–6, odds ratio [OR], 1.03, 95% confidence interval [CI], 1.004–1.06, $p = 0.03$; and for mRS 3–6, OR, 1.03, 95% CI, 1.01–1.05, $p = 0.01$). The cut-off values of infarct growth discriminating between good and poor outcomes were 0.99 cm^3 for mRS 0–1 vs. 2–6 (area under curve, 0.685; $P < 0.001$) and 8.86 cm^3 for mRS 0–2 vs. 3–6 (area under curve, 0.736; $P < 0.001$).

Conclusions: Our present study findings show that infarct growth within a week of onset independently predicts 3-month clinical outcomes. This suggests that short-term changes in infarct volume may serve as a surrogate marker of long-term clinical outcomes after ischemic stroke.

1. Introduction

An accurate prognosis of acute ischemic stroke is important for establishing a long-term treatment plan. Moreover, prognostic information can be used to evaluate the efficacy of thrombolysis or neuroprotective drugs. Clinical variables such as age, severity, and stroke subtype have consistently been associated with clinical outcomes [1–3]. A simple, reliable and inexpensive imaging predictor may be useful if it can demonstrate long-term outcome or early treatment effect. In previous reports, recanalization of vessels and lesion volume were suggested as imaging predictors [4]. However, it is controversial whether the lesion volume at a single time point can predict the clinical outcome in a stroke patient [5–7].

Ischemic lesion size increases dynamically and substantially during the first few days after onset and slowly decreases during the subsequent 3 to 4 weeks [8–11]. Thus, a hyperacute lesion on initial diffusion-weighted imaging (DWI) does not indicate the final lesion size, and it is assumed that assessment of infarct growth is a more reliable predictor of clinical outcome than ischemic lesion size at a single time point. In this regard, previous studies have tried to investigate the association between infarct growth and various clinical outcomes,

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but have been limited to a retrospective design, specific stroke subtype (subcortical infarction) or treatment (thrombolysis) group, or a relatively small number of patients [12–16]. It remains unclear whether early infarct growth has predictive value for long-term prognosis in a large number of patients in routine clinical practice.

In our prospective study, we hypothesized that early infarct growth might be independently associated with long-term outcome in acute ischemic stroke patients and attempted to estimate a cut-off value of infarct growth for predicting a poor outcome.

2. Methods

2.1. Patients

Our current study was a prospective investigation of acute ischemic stroke patients admitted to the Stroke Unit of the Asan Medical Center between December 2004 and December 2006. We screened consecutive patients who had (1) acute ischemic stroke confirmed by initial MRI including DWI and MR angiography within 24 h after onset, (2) a follow-up DWI scan performed at 5 (±1) days after symptom onset and (3) clinical follow-up for 3 months. Patients who had contraindications to MRI were excluded. The onset time was defined as the time patients were last known to be without neurological symptoms. This study was approved by the institutional review board of Asan Medical Center, and each patient or legal guardian provided written informed consent to participate in the study.

2.2. Imaging protocol and analysis

MRI examinations were performed using a 1.5-T MR imaging unit (Signa; GE Medical Systems, Milwaukee, WI) with echo-planar capabilities. The initial MRI protocol included DWI, fluid-attenuated inversion recovery imaging (FLAIR), gradient echo T2-weighted imaging (GRE), perfusion-weighted imaging, 3D time-of-flight MRA, and 3D contrast-enhanced MRA. The follow-up MRI protocol at 5 (±1) days after onset included DWI, GRE, and FLAIR in all patients. The detailed MRI protocol has been previously described [17].

The infarct volumes on DWI were measured by an investigator (S.M.K.) who was blind to the clinical data. The infarct volume was measured on DWI as the sum of the infarct area in each slice multiplied by the slice thickness with the use of the Picture Archiving and Communication System at the Asan Medical Center. Early infarct growth was defined as the absolute difference between the follow-up infarct volume and the baseline infarct volume.

2.3. Clinical assessment

Stroke severity at admission was measured by the National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtypes were determined according to the classification of the Trial of the Org 10172 in Acute Stroke Treatment (TOAST) [18]. Clinical outcomes were rated according to the modified Rankin Scale (mRS) at 3 months and were assessed by a certified research coordinator who was blind to the imaging and other clinical data. Clinical outcomes were dichotomized as (1) excellent (mRS 0–1) or poor (mRS 2–6) and (2) independent (mRS 0–2) or poor (mRS 3–6).

2.4. Statistical analysis

We analyzed the relationship between early infarct growth and clinical outcome at 3 months. We also compared demographics, risk factors for stroke, initial NIHSS scores, stroke subtypes, initial glucose levels, reperfusion therapy, and baseline infarct volumes between patients with good and poor outcomes according to the clinical outcome criteria. Continuous or numerical variables were expressed as the mean (standard deviation) or median (interquartile range [IQR]) and were compared by using a Student's *t*-test or Mann–Whitney *U* test. Categorical variables were analyzed by a chi-square test or Fisher's exact test. A multivariate logistic regression analysis considering all variables was then conducted to assess the independent association of the infarct growth with clinical outcome. Infarct growth was considered as a continuous variable in univariate and multivariate analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Finally, we estimated the cut-off value of infarct growth for predicting poor clinical outcome at 3 months using receiver operating characteristic (ROC) analysis. The cut-off value of infarct growth was regarded as the value that had a maximum sum of sensitivity and specificity. In addition, we further evaluated the association of early infarct growth and clinical outcome after excluding the patients with small-vessel occlusion. All statistical analyses were performed with SPSS 20.0 for Windows (IBM Corp., Armonk, NY) and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and infarct growth

During the study period, we screened 1351 patients with acute ischemic stroke. Of these patients, 942 were excluded (570 patients underwent initial DWI after 24 h, 96 patients did not provide study consent, 184 patients did not undergo follow-up DWI, 76 patients had a contraindication for the MRI, and 16 patients were excluded due to loss to follow-up at 3 months). Thus, 409 patients (253 men) were included in the final analysis, with a mean age (standard deviation) of 63.6 (12.0) years. The median NIHSS score was 5 (IQR, 2–8). Because lesion volumes were not normally distributed, we used median value for analysis and expressed both median and mean values in the tables. The median infarct volume was 1.00 cm^3 (IQR, 0.32–7.40) at baseline and 2.29 cm^3 (IQR, 0.61–17.07) at follow-up, resulting in a median infarct growth of 0.63 cm^3 (IQR, 0.11–6.33). Some degree of infarct growth was observed in 345 patients (84.4%). In 61 patients (14.9%), the infarct was smaller at follow-up than at baseline. In trend analysis, the infarct growth became larger as the mRS score increased (Fig. 1; $P < 0.001$).

3.2. Predictors of poor clinical outcomes

At the 3-month follow-up, 53.1% and 74.1% of patients had excellent and independent outcomes, respectively. Univariate analysis demonstrated that a larger baseline infarct volume and larger infarct growth

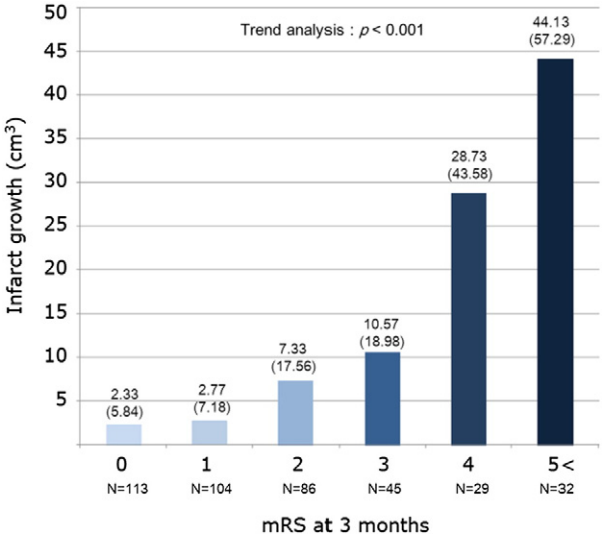

Fig. 1. Association between infarct growth and mRS at 3 months. mRS, modified Rankin Scale. Infarct growth is presented as mean (standard deviation).