Is Early Ischemic Lesion Volume on Diffusion-Weighted Imaging an Independent Predictor of Stroke Outcome? A Multivariable Analysis

Vincent N. Thijs, MD; Maarten G. Lansberg, MD; Christian Beaulieu, PhD; Michael P. Marks, MD; Michael E. Moseley, PhD; Gregory W. Albers, MD

Background and Purpose—The heterogeneity of stroke makes outcome prediction difficult. Neuroimaging parameters may improve the predictive value of clinical measures such as the National Institutes of Health Stroke Scale (NIHSS). We investigated whether the volume of early ischemic brain lesions assessed with diffusion-weighted imaging (DWI) was an independent predictor of functional outcome.

Methods—We retrospectively selected patients with nonlacunar ischemic stroke in the anterior circulation from 4 prospective Stanford Stroke Center studies evaluating early MRI. The baseline NIHSS score and ischemic stroke risk factors were assessed. A DWI MRI was performed within 48 hours of symptom onset. Clinical characteristics and early lesion volume on DWI were compared between patients with an independent outcome (Barthel Index score ≥85) and a dependent outcome (Barthel Index score <85) at 1 month. A logistic regression model was performed with factors that were significantly different between the 2 groups in univariate analysis.

Results—Sixty-three patients fulfilled the entry criteria. One month after symptom onset, 24 patients had a Barthel Index score ≥85 and 39 had a Barthel Index score <85. In univariate analysis, patients with independent outcome were younger, had lower baseline NIHSS scores, and had smaller lesion volumes on DWI. In a logistic regression model, DWI volume was an independent predictor of outcome, together with age and NIHSS score, after correction for imbalances in the delay between symptom onset and MRI.

Conclusions—DWI lesion volume measured within 48 hours of symptom onset is an independent risk factor for functional independence. This finding could have implications for the design of acute stroke trials. (Stroke. 2000;31:2597-2602.)

Key Words: magnetic resonance imaging, diffusion-weighted stroke, acute stroke outcome

A ccurate prediction of functional outcome after ischemic stroke is difficult because of the significant heterogeneity of stroke. Numerous predictors of functional outcome have been proposed.1 The most robust prognostic indicators are the age of the patient and the severity of the initial insult as measured with a neurological deficit scale such as the National Institutes of Health Stroke Scale (NIHSS).2–5 Ischemic stroke due to small-vessel intracranial disease is generally associated with a better outcome than other stroke subtypes, while prestroke disability and a previous history of stroke are associated with poorer outcomes.3,6–8

With the advent of diffusion-weighted imaging (DWI), determination of the volume of the early ischemic lesion is possible.9–11 DWI-measured volumes at acute time points correlate well with the final stroke volume as measured on T2-weighted MRI and with the Barthel Index determined at 30 to 120 days.12–15 It is unclear whether the volume of the early DWI lesion is an independent predictor of functional outcome.

Some authors suggest that the prediction of clinical outcomes after ischemic stroke can be improved by using a combination of clinical parameters and imaging parameters, such as the location and volume of the ischemic lesion.3,16 Recently, CT-measured ischemic stroke volume was found to be an independent predictor of outcome.3,16,17 Accurate measurement of the ischemic stroke volume with CT is only possible at subacute time points. If neuroimaging parameters, such as the volume of ischemic stroke, are to influence clinical management or to be used as selection criteria for clinical trials, an accurate determination of the ischemic volume soon after symptom onset is required.2,17,18

The aim of this study was to determine whether the volume of the ischemic lesion, as determined by DWI performed early after symptom onset, was an independent predictor of outcome in a multivariable model.
Subjects and Methods

Patients and Methods

Case report forms from all patients who participated in 4 prospective studies assessing the utility of DWI performed at the Stanford Stroke Center between 1996 and 1998 were evaluated for inclusion in this retrospective study.\textsuperscript{15,19,20} Patients were enrolled in these studies if they had a clinical diagnosis of definite or suspected acute cerebral infarction within 48 hours. Symptoms were required to be present >1 hour. A measurable clinical deficit (NIHSS score $\geq 1$) had to be present at the time of entry in the study. Patients were required to undergo $\geq 2$ MRI scans and were excluded from these studies if any coexisting or terminal systemic disease was present that limited life expectancy to $< 30$ days. Patients with dementia, a psychiatric disorder, or a substance abuse disorder that might interfere with the conduct of the study were excluded. Patients with a severely reduced level of consciousness were not eligible. Patients gave informed consent to be included in all studies. The study was approved by the Stanford University Institutional Review Board. From this database, we retrospectively selected the patients with the following characteristics: (1) acute ischemic stroke in the anterior circulation; (2) DWI performed within 48 hours of symptom onset; (3) NIHSS available at the time of initial MRI; and (4) clinical outcome measured at 1 month with the Barthel Index or the Rankin Scale (patients who died within 30 days were assigned a score of 0 on the Barthel Index and a score of 6 on the Rankin Scale).

Exclusion criteria were as follows: (1) prestroke history of disability (Rankin score $> 1$) or dementia; (2) final diagnosis of transient ischemic attack; (3) stroke subtype of small-vessel disease (according to Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria [clinical syndrome typical of small-vessel disease and lesion with maximal diameter $< 1.5$ cm or absence of lesion] at discharge)$^{22}$; and (4) absence of DWI hyperintensity on initial scan.

The NIHSS and the Barthel Index scores were determined by neurologists with expertise in the administration of these scales.\textsuperscript{23} Stroke onset was defined as the last time the patient was known to be without neurological deficit. The TOAST classification was used for classifying stroke etiology.\textsuperscript{21}

Patients who received intravenous recombinant tissue plasminogen activator (rtPA) or intra-arterial rtPA as well as patients who were enrolled in trials of neuroprotective agents were included.

We dichotomized stroke outcome as independent outcome (Barthel Index score $\geq 85$) and dependent outcome (Barthel Index score $< 85$). The cutoff value of $\geq 85$ on the Barthel Index was prespecified because it is clinically meaningful. Patients with these scores generally have an independent functional outcome, requiring only minimal or no assistance with daily activities.\textsuperscript{24,25}

Magnetic Resonance Imaging

MRI was performed with the use of echo planar imaging on a 1.5-T General Electric Signa magnet. Multislice whole-brain DWI was performed with the following parameters: 16 slices; repetition time, 8100 ms; echo time, 110 ms; slice thickness, 5 mm; gap, 2.5 mm; matrix, $128 \times 128$; and field of view, 24 cm; $b$ values were 0 and 741 s/mm$^2$. DW images were acquired in the x, y, and z directions. The x-, y-, and z-direction DW scans were averaged to minimize hyperintensities due to anisotropic water diffusion. Echo planar imaging diffusion images were processed to generate average (trace) apparent diffusion coefficient maps.

The lesion volumes were determined offline after the images were transferred to an image analysis software package (MRVision Software, MRVision Company).

Two observers (M.G.L. or C.B. and V.N.T.) manually outlined the area of diffusion hyperintensity and determined the volume by multiplying the areas of diffusion hyperintensity by the interstice gap. The results of the 2 observers were averaged.

Statistical Analysis

The clinical characteristics of patients with independent outcome and dependent outcome were compared in univariate analysis by Student’s $t$ test for continuous variables with a normal distribution or the Mann-Whitney $U$ test for characteristics with a nonnormal distribution and the $\chi^2$ test for categorical variables. Factors analyzed were age; sex; previous stroke; history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, smoking; previous carotid endarterectomy; delay between symptom onset and MRI; initial DWI lesion volume; and treatment (rtPA, neuroprotective agent or placebo) received. Spearman’s rank correlations were determined between acute DWI volume, acute NIHSS score, and Barthel Index score.

Factors significant at $P < 0.10$ were included in the logistic regression analysis. Characteristics with skewed distributions were normalized for the logistic regression analysis. The NIHSS score was considered a continuous variable, rather than a categorical variable, in the logistic regression analysis because of the limited number of patients. No interaction terms were included in the prognostic model to avoid overfitting. No stepwise procedure was performed. The logistic regression analysis calculates the individual probabilities (with values between 0 and 1) using the patient’s individual values for ischemic lesion volume, age, NIHSS score, and imaging delay. Individual patients with calculated probabilities above a particular cutoff (eg, 0.50) are predicted to belong to the dependent outcome group and patients below this cutoff value to the independent outcome group. All data were analyzed with SPSS 10.0.

Results

Ninety-seven patients fulfilled the inclusion criteria for the study. Six patients with a prestroke disability were excluded, as were 11 patients with a transient ischemic attack. Eight patients had a final stroke subtype diagnosis of small-vessel disease, and 9 patients did not have a hyperintensity on DWI. The 63 remaining patients were included in all analyses. The mean age of the patients was 72 years. Sixty-two percent of the patients were women. The median baseline NIHSS score was 7 (interquartile range, 3 to 13). According to the TOAST classification, the stroke subtype was large-artery atherosclerosis in 10 patients (16%) and cardioembolic in 22 patients (35%). Six patients (10%) had a stroke of other determined etiology. The stroke was considered cryptogenic in 25 patients (40%). One patient had acute lesions in both the anterior cerebral artery and middle cerebral artery territories. Thirteen patients were enrolled in investigational trials of neuroprotective agents and were randomized to either an investigational agent or a placebo. The neuroprotective agents tested were aptiganel hydrochloride ($n = 3$), citicoline ($n = 2$), fibroblast growth factor ($n = 2$), lubeluzole ($n = 2$), and nalmefene ($n = 4$). Seven patients received intravenous rtPA according to the guidelines of the National Institute of Neurological Disorders and Stroke. Two patients were treated with a combination of lubeluzole (or placebo) and intravenous rtPA. One patient was treated with intra-arterial rtPA. The median time between symptom onset and MRI was 18.9 hours (interquartile range, 5.5 to 33.9 hours). The median lesion volume on DWI was 12.4 cm$^3$ (interquartile range, 6.6 to 55.5 cm$^3$).

The clinical characteristics of the patients are detailed in Table 1. Four patients (6%) died within 30 days of stroke onset. The outcome was determined after a median of 31 days (interquartile range, 29 to 37 days) in the patients who survived. There was no difference in the times the outcomes were assessed in patients with a dependent outcome compared with patients with an independent outcome ($P = 0.51$). Thirty-nine patients (62%) had a Barthel Index score $\geq 85$, and 24 (38%) had a Barthel Index score $< 85$. The median
Barthel Index score was 25 (interquartile range, 5 to 65) in the group with Barthel < 85 and was 100 (25th percentile, 95) in the independent outcome group. In a univariate analysis, age, NIHSS, imaging delay, and DWI volume were significantly different between the patients with independent outcome and dependent outcome. These factors were included in the logistic regression analysis. A higher proportion of patients in the dependent outcome group was enrolled in neuroprotective agent studies. None of the neuroprotective agents evaluated in these patients have been demonstrated to improve clinical outcome, and therefore treatment status was not used as a covariate in the logistic regression analysis. Treatment with rtPA may decrease DWI volumes and improve clinical outcome.26 The number of patients treated with rtPA was similar in both groups and was not used as a covariate.

The baseline NIHSS score and DWI lesion volume correlated significantly with the 1-month Barthel Index (Spearman rank correlation \(-0.679, P<0.001\) for NIHSS and \(-0.504, P=0.004\) for volume of DWI hyperintensity). The baseline NIHSS score and the DWI lesion volume correlated significantly (Spearman rank correlation 0.454, \(P<0.01\)). The results of the logistic regression analysis are shown in Table 2. The model \(\chi^2\) was 30.45 (\(P<0.001\)). The Hosmer-Lemeshow test (\(\chi^2=9.7, P=0.288\)) was not significant, indi-
TABLE 2. Logistic Regression Analysis (n=63): Predictors of Dependent Outcome Defined as a Barthel Index Score <85

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in decades)</td>
<td>2.14</td>
<td>1.15</td>
<td>4.01</td>
<td>0.017</td>
</tr>
<tr>
<td>Log DWI volume, mm³</td>
<td>3.68</td>
<td>1.02</td>
<td>13.21</td>
<td>0.046</td>
</tr>
<tr>
<td>Log NIHSS score</td>
<td>13.6</td>
<td>1.2</td>
<td>154.6</td>
<td>0.036</td>
</tr>
<tr>
<td>Log imaging delay, h/min</td>
<td>0.33</td>
<td>0.49</td>
<td>2.24</td>
<td>0.257</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td>0.120</td>
<td></td>
</tr>
</tbody>
</table>

—2 log likelihood 53.281.

The following formula can be used to calculate the probabilities of a dependent outcome using the logistic model: Calculated probability = 1/\(1 + e^{-2.407 + 0.920 \times \text{age} + 1.303 \times \log(\text{DWI volume}) + 2.904 \times \log(\text{NIHSS}) - 1.104 \times \log(3600) + \log(Delay) - 8.739}\).

Discussion

The volume of DWI hyperintensity as measured within 48 hours of anterior circulation nonlacunar stroke proved to be an independent predictor of outcome. As reported previously, age and NIHSS score were also independent predictors of outcome.5

Previous studies have shown that the volume of the ischemic lesion determined by DWI is a univariate predictor of outcome.12,15,27,28 Baird et al29 reported that, along with age, NIHSS score, and delay between symptom onset and MRI, the volume of DWI obtained within 48 hours of ischemic stroke onset was an independent predictor of outcome. Saunders et al30 found that the volume of infarction on T2-weighted MRI determined 72 hours after symptom onset was predictive of functional outcome in a univariate analysis of 23 patients with a middle cerebral artery territory stroke. Pereira et al31 studied 31 patients and found in a logistic regression analysis that the stroke volume as determined by T2-weighted imaging and the N-acetyl aspartate ratio were predictive of functional outcome. Other studies have found that ischemic stroke volume as measured on CT between days 7 and 11 was a predictor of functional outcome in univariate analysis and in multivariable analysis.17,32–35

These data could potentially be used in a clinical trial to exclude patients with a very high probability of a good outcome or a bad outcome. In clinical trials, it is important to create treatment groups that are similar with respect to variables that affect functional outcome. The ischemic lesion volume on DWI could be used to help optimally balance treatment groups in clinical trials. Small imbalances in baseline characteristics between 2 treatment groups can bias the results obtained from a trial unless appropriate adjustments are made for differences in prognostic baseline variables.

Another potential application of DWI is as a surrogate marker in clinical trials. Temple36 defined a surrogate end point in a clinical trial as a laboratory measurement that is used as a substitute for a clinically meaningful end point. Changes induced by a therapy on a surrogate end point are expected to reflect changes in the clinically meaningful end point. In animal research on stroke, a reduction in ischemic lesion volume with the use of a neuroprotective or thrombolytic drug is used as the primary evidence of efficacy. Ischemic lesion volume is typically used as a surrogate marker of treatment efficacy in experimental stroke models because clinical measurements in animals are very difficult. To be used as an end point, the surrogate marker should be tightly linked to the outcome characteristic. The correlation value of −0.504 found between the ischemic lesion volume on DWI and the final Barthel Index score indicates some (albeit weak) linkage between the volume of the early DWI and the clinical outcome. The weak correlation can likely be attributed to both the numerous additional factors that influence functional outcome and the relative inadequacy of functional outcome scales. In addition, lesions of similar volume in different brain regions have variable influences on outcome.

Our multivariable model further supports a linkage between the volume of the ischemic lesion and functional outcome. Together these data support the notion that the ischemic lesion volume as defined by DWI should be further investigated as a potential surrogate end point in phase II clinical trials.17,37 For instance, a comparison of DWI lesion volumes before and after treatment in a placebo group and an active treatment group could be used as indirect evidence of
the efficacy of a potential drug or intervention. This analysis could be performed rapidly after stroke onset and potentially lead to a reduction in the cost of performing a phase II trial by limiting the sample size required and the time of follow-up needed. An objective analysis of lesion volumes early after stroke onset is also not affected by factors that can influence functional outcome, such as social circumstances or the quality of rehabilitative treatment. These factors are very difficult to control in small samples and can bias the results of a small trial. An objective measurement, such as a reduction in ischemic lesion size, could demonstrate a proof of the principle on which the experimental treatment was based.

There are several limitations to this study. We were not able to include all variables that have previously been reported to predict stroke outcome because of our small sample size. Important imbalances between the 2 groups were excluded with univariate analysis. We cannot, however, exclude the presence of suppressor variables, which can mask an independent predictor of outcome in an univariate analysis. Ten patients were treated with thrombolytic agents, and 13 patients were randomized to receive an investigational neuroprotective agent or a placebo shortly before the MRI was performed, and this could have biased the results of the analysis. Models derived from logistic regression tend to be overly optimistic. These models are generally less accurate when applied to another data set. Our data therefore await independent confirmation in a larger sample. Our patient sample is not representative of the patients typically enrolled in acute stroke treatment trials. In those trials, the time window for inclusion is shorter (<6 to 12 hours), the average stroke severity is greater, a higher proportion of patients are male, the outcome is usually determined at 3 or 6 months, and the reported ischemic stroke volumes as measured by CT at subacute time points are larger. The population of patients who agree to participate in MR trials might also not be representative of the general stroke population.

Our group and others have shown that ischemic lesions as assessed by DWI often increase in size during the first few days after symptom onset. Ischemic lesion volumes typically increase over time and reach a maximum at 72 to 96 hours. In the logistic regression analysis, we corrected for differences in the delay between symptom onset and MRI. Twenty-five percent of the patients were imaged before 6 hours, and these patients might have had larger lesions if imaged later. The optimal time point to perform MRI to predict stroke outcome is unknown. Very early imaging might underestimate the ischemic volume that is likely to best predict functional outcome because the lesion has not reached its final size. At subacute time points, vasogenic edema may be artificial or increase the lesion size. At chronic time points, atrophy might underestimate the actual stroke volume.

This study suggests that DWI lesion volume measured within 48 hours is an independent predictor of functional independence. The findings should be confirmed in a population more representative of the patients who are typically enrolled in acute stroke trials.

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