Risk Assessment of Symptomatic Intracerebral Hemorrhage After Thrombolysis Using DWI-ASPECTS

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Background and Purpose—Pretreatment lesion size on diffusion-weighted imaging (DWI) is a risk factor for symptomatic intracerebral hemorrhage (sICH) associated with thrombolytic treatment. Here, we investigated whether the Alberta Stroke Programme Early CT Score (ASPECTS) applied to DWI images (DWI-ASPECTS) predicts sICH risk accurately.

Methods—In this retrospective multicenter study, prospectively collected data of 217 patients with anterior circulation stroke treated with intravenous or intraarterial thrombolysis within 6 hours after symptom onset were analyzed. Pretreatment DWI-ASPECTS scores were assessed by 2 independent investigators. For bleeding risk analysis, DWI-ASPECTS scores were either categorized into 0 to 7 (n = 110) or 8 to 10 (n = 112) or in 3 groups of similar sample size (DWI-ASPECTS 0 to 5 [n = 69], 6 to 7 [n = 70], and 8 to 10 [n = 78]).

Results—DWI-ASPECTS scores correlated well with the DWI lesion volume (r = 0.77, P < 0.001, Spearman Rank test). Interobserver reliability for the assessment of DWI-ASPECTS was moderate (weighted kappa 0.441 [95% CI 0.373 to 0.509]). Twenty-three (10.6%) patients developed sICH. The sICH rate was significantly higher in patients with DWI-ASPECTS scores 0 to 7 (n = 21, 15.1%) as compared to patients with DWI-ASPECTS scores 8 to 10 (n = 2, 2.6%, P = 0.004). sICH risk was 20.3%, 10%, and 2.6% in the 0 to 5, 6 to 7, and 8 to 10 DWI-ASPECTS groups, respectively. DWI-ASPECTS remained an independent prognostic factor for sICH after adjustment for clinical baseline variables (age, NIHSS, time to thrombolysis).

Conclusions—DWI-ASPECTS predicts sICH risk after thrombolysis and may be helpful to contributing to quick sICH risk assessment before thrombolytic therapy. (Stroke. 2009;40:2743-2748.)

Key Words: stroke • acute • thrombolysis • diffusion weighted imaging • intracerebral hemorrhage • ASPECTS score

Several CT and MRI parameters were identified as markers of an increased risk of symptomatic intracerebral hemorrhage (sICH) after thrombolytic therapy for acute stroke.1–5

The size of the initial DWI lesion in MRI was recently recognized as an independent risk factor for sICH after thrombolytic therapy.4,5 Despite the high sensitivity and excellent interrater agreement of DWI for the detection of early ischemic changes (EIC),6 the assessment of exact DWI lesion volumes, ie, by manual volumetry is time consuming and therefore impractical in the acute stroke setting. Instead, a more rapid approximation of the extent of the DWI lesion would be preferable.

For CT imaging, a quick and standardized CT scoring system using predefined criteria (Alberta Stroke Programme Early CT Score [ASPECTS]) was successfully developed to improve interrater reliability for the detection of EIC.7 Furthermore, low ASPECTS scores on CT are predictive for a poor neurological outcome and are associated with an increased risk of sICH after thrombolytic therapy.7

Recently, it was shown that the ASPECTS scoring system can be applied to DWI images (DWI-ASPECTS), but data on the prediction of sICH using DWI-ASPECTS are lacking.8 The aim of the present study was to determine the prognostic value of DWI-ASPECTS concerning the sICH risk after thrombolytic therapy.

Patients and Methods

Patients

This multi-center analysis was performed based on data provided by 4 well-established academic stroke centers (Frankfurt, Hamburg,
The study was part of a larger project conducted as an initiative of the MR Stroke Study group (www.mrstroke.com) investigating risk factors for thrombolysis-associated sICH. Each of the centers participating in the current study uses standardized MRI protocols for acute stroke patients, approved by all local ethics committees.

Patients were included in the current analysis if (1) they presented with clinical signs of anterior circulation stroke, (2) thrombolytic therapy was administered within 6 hours of symptom onset, and (3) an MRI including DWI was performed before the initiation of treatment. Patients with MRI evidence of infarctions exclusively affecting the posterior circulation were excluded from further analysis. Symptomatic ICH was defined as in the NINDS trial (with only minor modifications), as CT- (or MRI-) documented hemorrhage that occurred within 36 hours after treatment onset and was temporally related to deterioration of the patient’s clinical condition in the judgment of the clinician. Additionally, a more strict sICH definition (any hemorrhage and NIHSS worsening /H11350 4 points) was used for a confirmatory analysis of the main findings. ICH volume was estimated using the ABC/2 formula. The following clinical variables that have shown to be associated with sICH were obtained for each patient: age, NIHSS score on admission, and time between symptom onset and thrombolytic treatment (categorized /H11021 3 hours, 3 to 6 hours). Data on antiplatelet use before hospitalization and on systolic and diastolic blood pressure at admission were available from about 65% of the patients.

Most patients were treated with standard intravenous tissue plasminogen activator (tPA) therapy (n=140). Two smaller subgroups were treated with either (1) intraarterial thrombolysis (ia) (n=50) or (2) combined intravenous/intraarterial (iv+ia) treatment (n=27).

MRI Data Acquisition and Analysis
MRI scans were performed on 1.5T scanners, all equipped with echo-planar imaging (EPI) data acquisition capabilities. Stroke protocols were not entirely uniform in the 4 participating centers, but all included an axial EPI diffusion weighted sequence (DWI). There were no predefined MRI patterns (such as DWI/PWI mismatch), which were required for inclusion in the study. DWI lesion volume was measured by the participating stroke centers using locally available software.

Assessment of DWI-ASPECTS Scores
DWI-ASPECTS scores were assessed by 2 investigators, a neuroradiologist (W.K.) and a neurologist (M.C.H.) both blinded to clinical data except for the side of the clinically suspected ischemia. The investigators performed the assessment of the scores independently. A template of 2 axial DWI slices with markers for the 10 regions being scored by the DWI-ASPECTS was provided (Figure 1). In practice, each reader reviewed the entire sequence of DWI slices to determine the score. In patients with bilateral anterior circulation infarctions, only the DWI-ASPECTS score for lesions within the clinically affected hemisphere was assessed.

Statistical Analysis
The mean value of DWI-ASPECTS of both raters was used for further statistical analysis. For illustration purposes, Figure 2 depicts the DWI-ASPECTS of only 1 rater (M.C.H.) because the ASPECTS score is categorized and consists of integral numbers only. As the variables “DWI-ASPECTS” and “initial DWI volume” were not normally distributed (Kolmogorov-Smirnov-Test), the Mann–Whitney U test was used to test for statistically significant differences between groups. To control for multiple tests when comparing more than 2 groups, we applied the closing test procedure with Kruskal–Wallis test as global test. Using binary logistic regression analysis, we analyzed whether DWI-ASPECTS was an independent prognostic factor for sICH. For several analyses, DWI-ASPECTS was dichotomized (scores 0 to 7 versus scores 8 to 10), according to a cut-off which has been used previously in CT based studies. We additionally performed a separate analysis after categorization into 3 groups of similar sample size according to the DWI-ASPECTS score (group 1: n=69, DWI-ASPECTS 0 to 5; group 2: n=70, DWI-ASPECTS 6 to 7; group 3: n=78, DWI-ASPECTS 8 to 10). Nonintegral numbers...
of the mean DWI-ASPECTS score of the 2 raters were uprounded for categorization (ie, if the mean DWI-ASPECTS score was 7.5, the patient was categorized in the 8 to 10 DWI-ASPECTS group). For comparison of DWI-ASPECTS and manual volumetry for sICH prediction, manually assessed DWI lesion size was dichotomized in lesions $<100$ mL and $\geq100$ mL. This cut-off was chosen because $100$ mL roughly corresponds to an involvement of 1/3 of the MCA territory. Results were considered statistically significant at the 5% level. All values are given as median (25th, 75th percentile), unless otherwise stated. For statistical analysis the SPSS 15.0 software (SPSS Inc) was used. The weighted kappa statistics and the ROC analyses were calculated with SAS 8.02 and the ROC macro (version 1.7), both from SAS Institute.

**Results**

In total, 217 patients were included in the present analysis. Interobserver reliability for the assessment of DWI-ASPECTS was moderate (weighted kappa 0.441 [95% CI 0.373 to 0.509]). DWI-ASPECTS correlated well with DWI lesion volume ($r=0.77$, $P<0.001$, Spearman Rank test; Figure 2).

Twenty-three (10.6%) patients developed sICH; this was associated with parenchymal hematoma (PH) grade 2 in 17 patients; with PH grade 1 in 5 patients and with hemorrhagic infarction (HI) grade 2 in 1 patient. Median ICH volume was 49 mL (23–116). On univariate analysis, median DWI-ASPECTS scores were significantly lower in sICH patients (5 [3,6]) as compared to patients without sICH (7 [5,8], $P=0.001$, Table 1). Accordingly, the proportion of patients with DWI-ASPECTS scores of 0 to 7 was significantly higher in sICH patients as compared to patients without sICH (70% versus 46%, $P=0.032$; Table 1). sICH occurred in 2.6% of patients with DWI-ASPECTS scores 8 to 10 and in 15.1% of patients with DWI-ASPECTS scores 0 to 7 ($P=0.004$).

Figure 3 gives an overview of sICH rates as a function of the DWI-ASPECTS score after grouping patients into 3 similarly sized groups. Patients with DWI-ASPECTS scores 0 to 5 had a 20.3% risk of sICH as compared to a 10% risk in patients with DWI-ASPECTS scores 6 to 7 and a 2.6% risk in patients with DWI-ASPECTS scores 8 to 10. As expected, initial NIHSS score and initial DWI lesion volume were significantly higher in patients with subsequent sICH. The proportion of sICH patients treated in the 3- to 6-hour time window was higher as compared to patients treated within 3 hours.
Although this difference did not reach statistical significance (Table 1).

In a multivariate model (n=212), DWI-ASPECTS score was an independent prognostic factor when controlling for age, initial NIHSS score, and time to thrombolytic treatment (odds ratio (OR) 0.791 per 1 point increase [95% CI 0.659 to 0.949, P=0.012]; Table 2). Likewise, the dichotomized DWI-ASPECTS score (0 to 7 versus 8 to 10) was an independent risk factor in this multivariate model (OR 0.201 [95% CI 0.043 to 0.940, P=0.041]).

Table 3 provides data on sensitivity, specificity, and positive and negative predictive values (PPV, NPV) for sICH prediction by 2 different dichotomized imaging criteria, DWI-ASPECTS scores 0 to 7 (versus scores 8 to 10) and DWI lesion size ≥100 mL (versus DWI lesions <100 mL). Sensitivity was high (0.91) for DWI-ASPECTS scores 0 to 7, whereas specificity was low (0.39). The opposite (low sensitivity, high specificity) was found for DWI lesions ≥100 mL. PPV was low for both parameters, most likely because of the small numbers of sICH. Remarkably, NPV was high (0.97) for DWI-ASPECTS scores 0 to 7. Using a ROC analysis, the area under the curve (AUC) did not differ significantly between DWI-ASPECTS (0.687 [95% CI 0.575 to 0.798]) and DWI lesion size (0.691 [95% CI 0.575 to 0.808]), indicating that both methods are significantly predictive for sICH. In the subgroup of patients being treated with iv tPA within 3 hours (n=115), sICH rate was 6.1%. PPV and NPV of the dichotomized DWI-ASPECTS were 0.09 and 0.98, being similar to the values of the whole patient population.

Using a more strict definition of sICH (PROACT II criteria) resulted in a substantially lower sICH rate (6.9%, n=15) but did not influence the major findings of the study: Patients with subsequent sICH according to the PROACT II criteria had significantly lower DWI-ASPECTS scores (sICH: 5 [3.6] versus no ICH: 7 [5.8], P=0.002). The sICH risk was 14.5% (n=10) for DWI-ASPECTS scores 0 to 5, 5.7% (n=4) for DWI-ASPECTS scores 6 to 7 and 1.3% (n=1) for DWI-ASPECTS scores 8 to 10 (P=0.002 between 0 to 5 and 8 to 10 DWI-ASPECTS group). Using the PROACT II sICH-criteria, DWI-ASPECTS remained an independent risk factor when controlling for the factors mentioned above (OR 0.722 per 1 point increase [95% CI 0.581 to 0.897, P=0.003]).

**Discussion**

The present study confirms the applicability of the ASPECTS scoring system to diffusion weighted images in terms of a high correlation with manual DWI volumetry and moderate interrater agreement. DWI-ASPECTS predicts sICH after thrombolytic therapy. Lower DWI-ASPECTS scores are associated with higher sICH rates.

The ASPECTS scoring system was initially developed to improve sensitivity and interrater reliability of EIC detection on CT scans. Both issues are of minor importance when transferring the ASPECTS system to DWI, because DWI is more sensitive than CT for EIC detection and has a higher interrater agreement. Nevertheless, the use of the ASPECTS system in DWI analysis may be beneficial for other reasons: DWI-ASPECTS is predictive for bad clinical short-term outcome. The sICH risk after thrombolysis is dependent on the pretreatment DWI lesion size. Although the “goldstandard” for the assessment of DWI lesion size is manual volumetry, this method is time consuming and impractical in a setting where quick decision making is needed. In contrast, ASPECTS—providing a somewhat semiquantitative estimate of the DWI lesion size—has been shown to be easy and quick to apply in the clinical setting and may therefore be of value for sICH risk approximation. Given the known strengths of DWI compared to non–contrast-enhanced CT imaging, DWI-ASPECTS may be superior to CT-ASPECTS for sICH risk assessment. However, this hypothesis needs confirmation by a direct comparison of both methods, which was out of the scope of the present study.

Despite the fact that patients with extensive EIC are at increased risk for sICH, it is still a matter of debate whether the presence of extensive EIC justifies exclusion from thrombolysis. A controlled trial would be needed to determine whether patients with extensive EIC, large DWI lesions, or low DWI-ASPECTS scores should be excluded from thrombolytic therapy. As a consequence, we do not recommend to not treat patients with thrombolytic therapy simply because of a low DWI-ASPECTS score. Furthermore, the ASPECTS rating system covers only 51% of the MCA territory overvaluing lesions within the striatocapsular region, whereas infarctions within the anterior cerebral artery territory are not covered at all by this rating system. Therefore, patients with similar lesion size may differ substantially in their ASPECTS scores. Proposals have been made to overcome this problem (ie, by the incorporation of explicit weights based on the spatial pattern of infarctions) but have not yet found their way into clinical routine.

We compared 2 potential risk markers on DWI concerning their usefulness in sICH risk approximation in patients receiving thrombolytic therapy, ie, (1) DWI-ASPECTS 0 to 7, and (2) DWI lesions ≥100 mL (determined by manual volumetry). Although sensitivity was high for dichotomized DWI-ASPECTS, its specificity was low, overestimating the
number of patients at risk for sICH, whereas DWI lesions \( \geq 100 \text{ mL} \) showed low sensitivity but higher specificity. These findings may in part be explained by the special nature of the DWI-ASPECTS score mentioned previously (ie, overestimating of striatocapsular infarcts). The low PPV of both methods is presumably attributable to the relatively low numbers of sICH but may also be attributable to a suboptimal cut-off for DWI-ASPECTS or DWI lesion size. However, both cut-off values were defined before data analysis. Of special interest is the very high NPV of DWI-ASPECTS. This translates to a very low sICH-risk (<3%) in patients with ASPECTS scores 8 to 10, probably the most useful finding of the present study in practical terms. Given the time consuming procedure for manual lesion volumetry and the known strengths of ASPECTS (good interrater agreement, quick applicability), DWI-ASPECTS may be favored for quick sICH risk approximation in acute stroke.

The main limitation of our analysis is the retrospective nature of the study. As a consequence, DWI-ASPECTS scores were not assessed in the acute clinical setting, prohibiting firm conclusions concerning the feasibility of the assessment of DWI-ASPECTS in real time. However, the feasibility and reliability of the assessment of CT-ASPECTS scores in real time has been demonstrated previously, and it is very likely that the same holds true for DWI-ASPECTS. Data on perfusion abnormalities were not systematically assessed, and the proportion of patients with a PWI/DWI mismatch is not known, although it is likely that the majority of patients being treated in the 3- to 6-hour time window had a PWI/DWI mismatch, which might have influenced the results. We dichotomized DWI-ASPECTS into scores of 0 to 7 and 8 to 10, according to previous CT based studies. Given the higher sensitivity of DWI for detection of early ischemia as compared to CT, it may therefore be possible that DWI-ASPECTS scores were generally somewhat lower (indicating “larger lesions”) as compared to CT-ASPECTS scores. We did not control for all established clinical and imaging predictors for sICH (ie, elevated blood pressure, antiplatelet use, leukoaraiosis) because these data were not available for the majority of patients. Therefore, the impact of DWI-ASPECTS for sICH risk approximation may have been overestimated in the present analysis.

In conclusion, DWI-ASPECTS predicts sICH risk after thrombolysis and may be one factor among others in quick risk assessment before thrombolytic therapy. A confirmation of our findings using a separate data set including established clinical and imaging risk factors is warranted.

Appendix

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Disclosures
None.

References
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