Original Contribution

Stroke Lesion Volumes and Outcome Are Not Different in Hemispheric Stroke Side Treated With Intravenous Thrombolysis Based on Magnetic Resonance Imaging Criteria

Amir Golsari, MD; Bastian Cheng, MD; Jan Sobesky, MD; Peter D. Schellinger, MD; Jens Fiehler, MD; Christian Gerloff, MD; Götz Thomalla, MD

Background and Purpose—Patients with right hemispheric stroke (RHS) have been reported to have a lower of good outcome after thrombolysis. We aimed at evaluating outcomes after stroke thrombolysis with regards to the affected hemisphere controlling for stroke lesion volume as a potential confounder.

Methods—We retrospectively analyzed data from a prospective study of patients with acute stroke treated with intravenous tissue-type plasminogen activator (tPA), based on magnetic resonance imaging criteria within 6 hours of symptom onset. Neurological deficit was assessed by the National Institutes of Health Stroke Scale. Lesion volume on acute perfusion imaging, diffusion-weighted imaging (DWI) and perfusion imaging/DWI mismatch were measured. Clinical outcome was assessed after 90 days using the modified Rankin Scale, and relation to affected hemisphere was studied by multivariate analysis.

Results—Of 173 patients, 55 (32%) presented with RHS, whereas 118 (68%) had left HS. Baseline National Institutes of Health Stroke Scale was lower in RHS (11.7 versus 13.6; \(P=0.031\)). There were no differences in DWI lesion volume (11.0 versus 17.8 mL; \(P=0.519\)), perfusion imaging lesion volume (98.9 versus 118.3 mL; \(P=0.395\)), perfusion imaging/DWI mismatch (60 versus 85.05 mL; \(P=0.283\)). Clinical outcome was also comparable for both groups (modified Rankin Scale, 0–1; \(P=0.327\)). In multivariate analysis, DWI lesion volume (\(P<0.001\)) and age were associated with modified Rankin Scale at day 90, whereas affected hemisphere was not.

Conclusions—We did not find differences between RHS and left HS with regards to stroke lesion volumes or outcome after thrombolysis. Previously reported hemisphere-related differences in stroke outcome may partly result from imbalances in stroke lesion volume between RHS and left HS. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.007292.)

Key Words: diffusion-weighted MRI · magnetic resonance imaging · outcome studies · perfusion-weighted MRI · stroke · thrombolytic therapy · tissue-type plasminogen activator

Ischemic stroke is one of the most common causes of death and the major reasons for permanent disability in adulthood. According to World Health Organization estimates, >15 million people experience stroke each year, and one third of these are left permanently disabled.1 Intravenous thrombolysis with recombinant tissue-type plasminogen activator (tPA) may alter this fate and has demonstrated to improve outcome in a relevant proportion of patients with stroke.2–4

Stroke symptoms and stroke outcome relate to location and size of the stroke lesion. In addition, the affected hemisphere seems to play a role both with regards to stroke symptoms, as well as management, and outcome of stroke, mostly favoring left hemispheric stroke (LHS). Patients with right hemispheric stroke (RHS) were reported to present later to the emergency department than patients with LHS.5–7 This has been interpreted as a result of the clinical characteristics of RHS, which frequently involves symptoms that are less clearly recognized by patients or relatives (e.g., neglect, visual perception disorders) or come along with anosognosia. As a consequence, patients with RHS were also observed to have a lower chance of receiving treatment with intravenous tPA.5,7 Moreover, outcome studies have reported worse functional outcome in patients with RHS when compared with those with LHS.8,9 Finally, an interaction of treatment with intravenous tPA and affected hemisphere was reported with patients with LHS having a 2-fold increased likelihood of good outcome at 3 months after thrombolysis than patients with RHS.7

We aimed at evaluating baseline clinical and imaging characteristics and outcome with regards to the affected hemisphere in patients with stroke treated with intravenous tPA based on magnetic resonance imaging (MRI) criteria, thus controlling for potential clinical and imaging confounders of possible side-related differences in outcome, such as stroke lesion volume.
Methods

In a retrospective analysis, we analyzed clinical and MRI data of 173 patients with stroke from a prospective, multicenter, observational study of patients with acute stroke treated with intravenous tPA, based on MRI criteria within 6 hours of symptom onset. In brief, this was a prospective study in which MRI, according to standardized protocol, was used to identify patients for treatment with intravenous tPA within expanded time window of 26 hours. Three stroke centers contributed data to this study (university hospitals Hamburg, Heidelberg, and Cologne). All patients with stroke from the original study were included in our study. Patients with bilateral or cerebellar stroke lesions were excluded from the study.

MRI studies were performed on a 1.5-T scanner (Magnetom Symphony/Sonata; Siemens, Erlangen, Germany), using a standardized stroke MRI protocol as reported previously. Lesion volumes on initial diffusion-weighted imaging (DWI), initial perfusion imaging (PI), and perfusion–diffusion mismatch volume and ratio were calculated. Details of the postprocessing procedures have been published previously. Administration of intravenous tPA within the first 3 hours of symptom onset followed the licensing criteria of Alteplase. After 3 to 6 hours, intravenous thrombolysis was performed as an individual decision based on MRI findings after informed consent. Neurological deficit on admission was assessed by the National Institutes of Health Stroke Scale. Lesion volume on initial DWI and PI was measured, and perfusion–diffusion mismatch volume (PI lesion volume–DWI lesion volume) and ratio were calculated. Clinical outcome was assessed after 90 days using the modified Rankin Scale (mRS). With the side of the acute stroke syndrome as the independent variable, group differences in the following parameters were evaluated: age, sex, National Institutes of Health Stroke Scale (NIHSS) at presentation, door-to-MRI time, door-to-needle time, initial DWI volume, initial PI volume, perfusion–diffusion mismatch, rate of symptomatic intracranial hemorrhage, and mRS after 90 days. According to the definitions used in Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), that is, local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurological deterioration, as indicated by a score on the NIHSS≥4 points than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death. A favorable outcome after stroke was defined as an mRS of 0 to 1 after 90 days. In addition, we tested for differences in mRS 0 to 2 and outcome distribution across the entire mRS scale (mRS shift analysis). All values are presented as median (interquartile range) for continuous variables and counts (percentage) for categorical variables. Group comparisons were made using the Mann–Whitney U test for continuous variables, Fisher exact test for categorical variables, and χ² test of difference in linear trends in ordinal mRS outcomes. Correlations between the variables were studied using the Spearman rank correlation. The Fisher z-transformation was used to test for differences in correlations between groups (SPSS 10; SPSS Inc). Multivariate regression analysis was used to test for differences in mRS at day 90 taking into account age, sex, side, DWI, and PI lesion volumes. As we observed collinearity between DWI lesion volumes and NIHSS (P=0.001), NIHSS was not included in the multivariate analysis.

Results

Of 173 patients with stroke, 55 (32%) presented with RHS, whereas 118 (68%) had LHS. The Table shows the results of group comparison between RHS and LHS. Patients with LHS presented with higher scores on the NIHSS (RHS: median, 12 [8.00–15.00] versus LHS median, 14 [interquartile range, 9.75–17.25]; P=0.031). No statistically significant differences were observed between groups for age (RHS, 65.00 [61.00–74.00] versus LHS, 63.50 [55.75–71.50]; P=0.376) or sex (RHS: f=34.6% versus LHS: f=43.3%; P=0.223).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RHS (n=55)</th>
<th>LHS (n=118)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>65.00 (61.00–74.00)</td>
<td>63.5 (55.75–71.50)</td>
<td>0.327</td>
</tr>
<tr>
<td>Women, %</td>
<td>34.6</td>
<td>43.3</td>
<td>0.223</td>
</tr>
<tr>
<td><strong>Baseline parameters median</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>12.00 (8.00–15.00)</td>
<td>14.00 (9.75–17.25)</td>
<td>0.031</td>
</tr>
<tr>
<td>Onset-to-MRI (time, min)</td>
<td>140.00 (105.00–177.00)</td>
<td>149.00 (109.50–195.00)</td>
<td>0.126</td>
</tr>
<tr>
<td>Onset-to-needle (time, min)</td>
<td>160.00 (120.00–205.00)</td>
<td>167.50 (133.75–210.00)</td>
<td>0.725</td>
</tr>
<tr>
<td><strong>MRI lesion volumetric, mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial DWI volume</td>
<td>11.00 (3.90–35.75)</td>
<td>17.78 (7.00–38.00)</td>
<td>0.519</td>
</tr>
<tr>
<td>Initial PI volume</td>
<td>98.90 (33.00–190.00)</td>
<td>118.30 (58.67–214.42)</td>
<td>0.395</td>
</tr>
<tr>
<td>PI/DWI mismatch volume</td>
<td>60.00 (16.20–155.66)</td>
<td>85.05 (29.30–176.25)</td>
<td>0.283</td>
</tr>
<tr>
<td>Mismatch volume ratio</td>
<td>4.97 (1.71–12.00)</td>
<td>5.20 (2.03–14.38)</td>
<td>0.634</td>
</tr>
<tr>
<td>Mismatch, %</td>
<td>81.8 (n=45)</td>
<td>86.4 (n=102)</td>
<td>0.494</td>
</tr>
<tr>
<td><strong>Outcome parameters, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>41.8 (n=28)</td>
<td>50.8 (n=60)</td>
<td>0.327</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>58.1 (n=32)</td>
<td>60.1 (n=72)</td>
<td>0.741</td>
</tr>
<tr>
<td>mRS 5–6</td>
<td>7.3 (n=4)</td>
<td>12.7 (n=15)</td>
<td>0.434</td>
</tr>
<tr>
<td>mRS 6</td>
<td>1.8 (n=1)</td>
<td>9.3 (n=11)</td>
<td>0.106</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1.8 (n=1)</td>
<td>2.5 (n=4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Responder after treatment</td>
<td>43.6 (n=24)</td>
<td>45.7 (54)</td>
<td>0.875</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; ICH, intracerebral hemorrhage; IQR, interquartile range; LHS, left hemispheric stroke; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PI, perfusion imaging; and RHS, right hemispheric stroke.
Furthermore, no significant differences were detected for the parameters time from symptom onset to the MRI examination (onset-to-MRI) (RHS, 140.00 [105.00–177.00] versus LHS, 149.00 [109.50–195.00]; \( P=0.126 \)) and time from symptom onset to thrombolytic treatment (onset-to-needle; RHS, 160.00 [120.00–205.00] versus LHS, 167.50 [133.75–210.00]; \( P=0.720 \)).

For the entire population, diffusion lesion volume of 27.15 mL (5.90–36.08) and perfusion lesion volume of 136.88 mL (48.23–210.83) were within the range of a typical population of patients with stroke treated with thrombolyis, and the vast majority of patients presented with a relevant mismatch between perfusion and diffusion lesion with a median mismatch volume of 109.73 mL (23.58–166.75) and a median mismatch ratio of 20.26 mL (1.98–13.78). There seemed to be a slight tendency toward larger diffusion and perfusion lesion volumes in LHS (Figure 1), but there were no significant differences between RHS and LHS with regards to diffusion lesion, perfusion lesion, and perfusion–diffusion mismatch.

In the outcome analysis, the proportion of patients with a favorable outcome as defined by an mRS score 0 to 1 was also similar for both groups (RHS: n=23; 41.8% versus LHS: n=60, 50.8%; \( P=0.327 \)). Proportion of patients with an mRS 0 to 2 was also comparable between hemispheres (RHS: n=32; 58.2% versus LHS: n=72; 61.0%, \( P=0.741 \)). MRS shift analysis revealed a comparable distribution of outcomes across the entire mRS (\( P=0.372 \); Table; Figure 2). In the multivariate analysis, acute DWI lesion volume (\( \beta=0.283; P=0.001 \)) and age (\( \beta=0.328; P=0.001 \)) were associated with mRS after 90 days, whereas sex, side of the stroke, and PI lesion volume were not. Finally, no differences were observed as to the frequency of symptomatic intracranial hemorrhage (RHS: n=1; 1.8% versus LHS: n=3; 2.5%; \( P=1.000 \)).

**Discussion**

We investigated differences in outcome after stroke thrombolysis related to the affected hemisphere by analyzing baseline clinical and imaging parameters, as well as outcome in a large sample of patients with stroke treated with intravenous tPA based on MRI findings. As a main finding, we did not identify differences in clinical outcome after thrombolysis between RHS and LHS. MRI lesion volumes were also comparable for both groups, whereas NIHSS scores on admission were higher in left hemispheric strokes.

Thus, we were unable to reproduce the results of previous studies reporting better clinical outcome after thrombolysis for LHS.\(^2\)\(^3\) Although our sample was comparable with the previously reported populations as to stroke severity, the main difference of our study when compared with previous reports was the use of MRI to guide thrombolysis, whereas in previous reports treatment was mainly based on CT findings. The availability of MRI in our sample enabled us to characterize our patient population with regards to stroke lesion volumes and to analyze acute perfusion and diffusion lesion volume as potential covariates of stroke outcome. Of note, although not statistically significant in our sample, acute stroke lesions volumes tended to be smaller in patients with RHS than in patients with LHS (Figure 1). This is different from previous studies where patients with RHS presented with significant larger lesion volumes.\(^4\) It has also been demonstrated that the use of multimodal MRI sequences enables reliable differentiation between infarcted and hypoperfused tissue at risk by the PI/DWI mismatch concept.\(^5\)\(^6\) In our work, we were able to quantify a corresponding mismatch area in 81.6% of patients with RHS and 86% of patients with LHS. Thus, by the selection of patients likely to respond to thrombolysis, we may have balanced baseline differences between RHS and LHS as to initial stroke lesion size resulting from the observed tendency of patients with RHS to present later to the emergency department.\(^5\)^\(^6\) Although in our sample both baseline imaging findings and outcome after thrombolysis were comparable between RHS and LHS, we may speculate that in previous studies differences in stroke outcome result from baseline differences in stroke lesion size which have not been studied.\(^7\)^\(^8\)\(^9\) We also demonstrated that initial DWI lesion volume are associated with clinical outcome after 90 days, which is consistent with previous findings of acute lesion volume being a strong predictor of clinical outcome.\(^10\)

As reported previously, we observed higher NIHSS scores in LHS with patients when compared with patients with RHS. Higher NIHSS scores in LHS have been observed frequently\(^5\)^\(^7\)^\(^11\) and are likely to result from the composition of the NIHSS and the differences in quality and extent of the...
clinical symptoms between the 2 hemispheres. Aphasia as a symptom related to stroke lesions in the language-dominant (mainly left) hemisphere scores much higher in the NIHSS than corresponding symptoms of the nondominant (mainly right) hemisphere, such as spatial-constructive disorders, neglect, anosognosia, and agnosia. This imbalance of the NIHSS is well known.17–21 It is also well known that stroke outcome is strongly linked to initial stroke severity. For this reason, we included clinical severity in multivariate analysis of the relationship between affected hemisphere and outcome. Also, this analysis did not reveal any difference in outcome between the affected hemispheres, whereas NIHSS was identified as a. Furthermore, we did not observe any differences in the frequency of symptomatic intracranial hemorrhage after treatment with recombinant tPA between RHS and LHS by selecting patients with MRI criteria.

In the present study, there are several limitations that must be considered. We identified patients for thrombolysis using multiparametric MRI. This leads to a highly selected population, which may not be fully comparable with patient’s samples from CT-based studies, especially resulting from the exclusion of patients with large acute DWI lesions, which are not seen, on plein computed tomography.22 In our sample, we observed an imbalance in the frequency of RHS and LHS with more than twice as many patients included with LHS. This is likely result from the fact that only patients with thrombolysis were included. Previous studies have reported lower rates of thrombolysis in RHS,2–7 likely resulting from clinical characteristics of right hemispheric lesions. We cannot infer on thrombolysis rates from our study because we did not systematically record data on the basic population of all patients with stroke treated in the participating centers during the study period. However, the number of patients with RHS treated in our observational was markedly smaller than the number of patients with LHS, which may reflect this effect observed in previous studies.

Conclusions

In this large stroke cohort, we did not find differences in outcome of stroke thrombolysis relating to the affected hemisphere. Previously reported hemisphere-related differences in stroke outcome may partly result from imbalances in stroke lesion volume between RHS and LHS, which were not present in our sample. Although there is no doubt that the affected hemisphere influences stroke symptoms and outcome, there is no reason to treat patients with RHS and LHS differently with regards to thrombolysis.

Acknowledgments

We thank all our colleagues from the Departments of Neurology and Neuroradiology, and medical and technical staff in the participating centers for their support.

Sources of Funding

The study was supported by the Kompetenznetzwerk Schlaganfall sponsored by the Bundesministerium für Bildung und Forschung (B5; No. 01GI9902/4).

Disclosures

Dr Fiehler has received fees as a consultant or lecture fees from Codman, Covidien, Siemens and Stryker. Dr Gerloff has received research grant from the European Commission (EU Grant FP7 278276). Dr Schellinger has received travel grants, consultant honoraria, expert activities (German Court), and lecture fees (all modest) in- and outside the scope of this article by Boehringer Ingelheim, Covidien, Bayer Vital, Glaxo Smith Kline, BMS, Sanofi Aventis, Cerevast, Photothera, Coaxia, Siemens. Dr Thomalla has received fees as a consultant or lecture fees from Covidien, Pfizer, Bayer health Care and Boehringer Ingelheim. Dr Sobesky has received consultant and speakers honoraria and travel fees from Boehringer Ingelheim. The other authors report no conflicts.

References


Stroke Lesion Volumes and Outcome Are Not Different in Hemispheric Stroke Side Treated With Intravenous Thrombolysis Based on Magnetic Resonance Imaging Criteria
Amir Golsari, Bastian Cheng, Jan Sobesky, Peter D. Schellinger, Jens Fiehler, Christian Gerloff and Götz Thomalla

Stroke. published online February 19, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/02/19/STROKEAHA.114.007292