Safety of Intravenous Fibrinolysis in Imaging-Confirmed Single Penetrator Artery Infarcts

Soo Joo Lee, MD; Jeffrey L. Saver, MD; David S. Liebeskind, MD; Latisha Ali, MD; Bruce Ovbiagele, MD; Doojin Kim, MD; Paul Vespa, MD; Michael Froehlicher, MD; Matthew Tenser, MD; Jignesh Gadha, MD; Sidney Starkman, MD

Background and Purpose—Hemorrhagic transformation (HT) after fibrinolytic therapy may be less common in patients with acute cerebral ischemia confined to single penetrator artery (SPA) territories than in patients with large artery ischemia. Previous investigations of HT diagnosed small vessel ischemia based on lacunar clinical syndromes, an approach known to yield misdiagnosis in one-third to one-half of cases.

Methods—Consecutive intravenous tissue plasminogen activator-treated patients in a prospectively maintained hospital registry were analyzed. Patients were classified as having SPA ischemia if they had imaging evidence of: (1) deep location; (2) diameter ≤1.5 cm; and (3) distribution in a single penetrator territory, regardless of presenting clinical syndrome. Lacunar clinical syndrome was defined according to the Oxfordshire Community Stroke Project classification.

Results—Among 93 intravenous tissue plasminogen activator-treated patients, mean age was 71.5, 62.4% were female, and median pretreatment National Institutes of Health Stroke Scale score was 14. Single penetrator artery ischemia was imaged in 13 (14.0%) and large artery ischemia was imaged in 75 (80.6%), with no visualized ischemic injury in 5 (5.4%). Lacunar clinical syndromes were present in 23 (24.7%), including 10 with SPA ischemia and 9 with large artery ischemia. No patient with imaging-confirmed SPA infarcts experienced any hemorrhagic transformation, whereas any radiological HT occurred in 29.3% of large artery infarcts (P=0.03). Symptomatic intracerebral hemorrhage occurred in 0% of SPA infarcts vs 4.0% of large artery infarcts.

Conclusion—HT after lytic therapy in imaging-confirmed SPA infarcts is uncommon. Imaging demonstration of ischemia confined to SPA territory better-identifies this population at low risk for hemorrhagic complications than clinical lacunar syndromes. (Stroke. 2010;41:2587-2591.)

Key Words: fibrinolysis ■ intracranial hemorrhage ■ lacunar infarction ■ tissue plasminogen activator

The risk of hemorrhagic transformation (HT) after fibrinolytic therapy for acute cerebral ischemia is related to the volume of ischemic tissue; therefore, HT may be less common in patients with ischemia confined to a single penetrator artery (SPA) territory than in patients with infarcts involving large artery or multiple artery territories. This hypothesis has not been reliably investigated previously, because prior studies of HT have diagnosed small vessel ischemia based on lacunar clinical syndromes, an approach that is known to yield misdiagnosis in one-third to one-half of cases. With the spread of multimodal MRI and CT, modern lytic treatment decisions are increasingly based on direct imaging delineation, rather than clinical inference, regarding site and size of arterial occlusion.

The purpose of this study was to determine the rate of HT after intravenous fibrinolysis in patients with imaging-confirmed SPA ischemia.

Patients and Methods

In a prospectively maintained hospital registry, consecutive patients were identified who were treated with intravenous tissue plasminogen activator (tPA) within 3 hours after the onset of symptoms at the University of California, Los Angeles Medical Center, from 1999 to 2008. Patients subsequently treated with combined intra-arterial fibrinolysis, angioplasty with stent, or mechanical clot disruption were excluded in this study.

Patients were then divided into 2 subgroups, SPA infarcts vs large artery or multiple artery territories (non-SPA) infarcts. This classification was based on the visualized topography of ischemia as delineated on all available sequences, including diffusion and perfusion MRI and noncontrast and perfusion CT. Patients were classified as having SPA infarcts if they had imaging evidence of: (1) deep location; (2) diameter ≤1.5 cm; and (3) distribution in SPA territory, regardless of the clinical syndrome, the presence of steno-occlusion in responsible arteries, and the presence of cardio-embolic, hypercoagulable, or other etiologic mechanisms.

Patients were also classified as exhibiting lacunar or nonlacunar clinical syndromes. Patients were considered to have lacunar clinical
syndromes if they presented with pure motor hemiparesis, pure sensory stroke, sensory motor stroke, dysarthria clumsy hand, or ataxic-hemiparesis using the classification algorithm of the Oxfordshire Community Stroke Project. All patients underwent control CT or MRI within 24 hours after tPA therapy and earlier imaging if clinical deterioration occurred. All scans performed at <36 hours were reviewed for the presence of HT. Postlytic radiological HT within the ischemic field was classified as hemorrhagic infarct-1, hemorrhagic infarct-2, parenchymal hematoma (PH)-1, and PH-2 using standard criteria. Symptomatic intracerebral hemorrhage (ICH) was defined, using the Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria, as the occurrence of an increase in the National Institutes of Health Stroke Scale score of ≥4 points in the setting of local or remote PH-2.

Image interpretation determining the presence of SPA and non-SPA infarcts was performed by an experienced stroke neurologist (S.J.L.) blinded to clinical data except for the side of clinically suspected ischemia. Lesion diameter ≤1.5 or >1.5 cm was estimated by diffusion-weighted imaging when MR images were available. The presence of HT on follow-up CT and MRI scans was rated by a stroke neurologist and a neuroradiologist. Interobserver agreement about the presence of HT was assessed using the κ statistic. Disagreements were resolved by a consensus discussion. For statistical analyses, we compared the mean between groups using the t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed variables. Normality was evaluated with the Kolmogorov-Smirnov test. Patient groups were compared by contingency tables for categorical variables with use of a x² test and Fisher exact test if the numbers of expected frequencies in each cell of the contingency table were >5. P<0.05 was considered statistically significant. Because at least 1 candidate predictor variable had no value, stepwise multivariate logistic analysis was performed using Monte Carlo simulation and then exact permutation methods to estimate model parameters (LogXact program, version 8; Cytel), with variable retention for P<0.05.

### Results

Among 134 patients treated with intravenous tPA during the study period, 93 met study entry criteria. The other 41 patients were excluded because they were treated with endovascular recanalization therapies after intravenous tPA, including clot retrieval (n=26), intra-arterial fibrinolysis (n=12), and angioplasty with stent (n=3). Among the 93 patients treated with intravenous tPA alone, mean±SD age was 71.5±15.8 years (range, 23–91), and 62.4% were female. The median National Institutes of Health Stroke Scale score before administration of intravenous tPA was 14.0 (interquartile range, 7–21). The median last-known well to treatment time was 150 minutes (range, 50–180). Demographic data, risk factors profiles, and initial laboratory data for these patients are shown in the Supplemental Table (available online at http://stroke.ahajournals.org).

Imaging performed before intravenous tPA infusion included noncontrast CT only in 58 patients, CT perfused blood volume imaging in 3, diffusion and perfusion MRI without CT in 22, and both noncontrast CT and diffusion and perfusion MRI sequences in 10. Postlytic follow-up imaging included CT only in 17 patients, MRI only in 8, and both CT and MRI in 68.

Of the 93 patients, 88 had acute ischemic changes visualized on imaging, whereas 5 showed no responsible acute lesion on initial and follow-up CT and/or MRI. Among these 5 patients, 4 showed complete clinical resolution of the symptoms (averted stroke) and the other had marked improvement with mild residual aphasia after thrombolytic therapy. Pretreatment diffusion and perfusion MRI was performed in 32 patients, permitting assignment to the categories of SPA or non-SPA infarct on the basis of pretreatment imaging alone in all instances. In the remaining 56 cases (60.2%), only noncontrast CT was performed before treatment, and SPA categorization was made based on imaging after treatment, which was generally multimodal MRI performed within the first 72 hours after presentation.

Acute ischemic changes confined to SPA territory were visualized in 13 patients (14.0%). Of the 13 patients, 8 had SPA infarct in internal capsule, 2 were in corona radiata, 2 were in thalamus, and 1 was in pons. The remaining 56 patients had acute ischemic changes in large artery territories (75; 80.6%) or no visualized ischemic injury (5; 5.4%). In 8 patients, SPA territory infarcts were visualized on pretreatment diffusion/perfusion MRI or perfusion CT. Post-treatment imaging did not alter SPA vs non-SPA categorization in any case undergoing pretreatment multimodal MRI or CT.

Lacunar clinical syndromes were present in 23 patients (24.7%), including 10 with sensory motor stroke, 8 patients with pure motor hemiparesis, 4 with dysarthria clumsy hand syndrome, and 1 with ataxic hemiparesis. Among patients with SPA infarcts, 10 had a clinical lacunar syndrome and 3 had nonlacunar syndrome. Among non-SPA infarct patients, 66 had nonlacunar syndrome and 9 had lacunar syndrome. The predictive value of a classical lacunar syndrome for identifying an underlying SPA infarct was sensitivity (76.9%; 95% confidence interval [CI], 46.2%–94.7%), specificity (85.3%; 95% CI, 75.3%–92.4%), positive predictive value (47.6%; 95% CI, 25.7%–70.2%), negative predictive value (95.5%; 95% CI, 87.5%–99.1%), and overall accuracy (84.1%; 95% CI, 76.5%–91.7%).

Postlytic radiological HT, ranging from small petechiae to parenchymal hematoma (hemorrhagic infarct or PH), was found in 22 patients (23.7%; Table 1). Inter-rater agreement for the presence of HT was high (κ=0.94). Symptomatic ICH occurred in 3 patients (3.2%). No patient with imaging-confirmed SPA infarcts experienced any HT, including no symptomatic ICH, no hemorrhagic infarct, and no PH; HT was observed only in patients with infarcts involving large or multiple artery territories. This difference reached statistical significance for the occurrence of any radiological HT, SPA infarcts (0%; 95% CI, 0%–14.5%) vs large artery infarcts (29.2%; 95% CI, 19.0%–39.6%; P=0.03). In the subgroup of 9 patients who presented with clinical lacunar syndromes but who were actually experiencing underlying large artery in-
farct, any radiological HT occurred in 3 patients (1 HT-1 and 2 PH-1; Table 2). Remote PH outside of the initially ischemic area occurred in 3 patients with non-SPA ischemia, symptomatic in 1 and asymptomatic in 2, and all were in patients 90 years or older (average age of remote PH vs non-remote PH patients, 91.7 vs 70.9 years; \( P < 0.006 \)).

Among 19 candidate predictor variables, in univariate analysis, SPA infarct and National Institutes of Health Stroke Scale score were the variables most strongly associated with reduced risk of HT (Supplemental Table). On multivariate analysis, 4 variables were selected for inclusion in the predictive model for the occurrence of any HT, with higher National Institutes of Health Stroke Scale score (odds ratio, 1.07; 95% CI, 0.99–1.15) and higher systolic blood pressure (odds ratio, 1.03; 95% CI, 1.00–1.06) increasing HT risk and presence of SPA infarct (odds ratio, 0.17; 95% CI upper limit, 1.17), and previous stroke history (odds ratio, 0.19; 95% CI, 0.12–1.18) decreasing HT risk. Clinical outcome at discharge varied among patients with different stroke subtypes, as shown in the Figure.

**Discussion**

This study confirms that patients with imaging-verified SPA ischemia are at low risk for HT after intravenous thrombolysis. No instances of even minor petechial hemorrhage were observed among the SPA infarct patients in this series. Multivariate analysis suggested that imaging-confirmed SPA ischemia was an independent predictor of reduced risk of HT.

No previous investigation has investigated the subset of patients with imaging-confirmed lacunar infarcts. Previous studies have analyzed the frequency of HT in patients with clinical lacunar syndromes, but a substantial proportion of these patients actually harbor underlying large artery infarcts. Among 19 candidate predictor variables, in univariate analysis, SPA infarct and National Institutes of Health Stroke Scale score were the variables most strongly associated with reduced risk of HT (Supplemental Table). On multivariate analysis, 4 variables were selected for inclusion in the predictive model for the occurrence of any HT, with higher National Institutes of Health Stroke Scale score (odds ratio, 1.07; 95% CI, 0.99–1.15) and higher systolic blood pressure (odds ratio, 1.03; 95% CI, 1.00–1.06) increasing HT risk and presence of SPA infarct (odds ratio, 0.17; 95% CI upper limit, 1.17), and previous stroke history (odds ratio, 0.19; 95% CI, 0.12–1.18) decreasing HT risk. Clinical outcome at discharge varied among patients with different stroke subtypes, as shown in the Figure.

**Table 2.** Classification of Stroke Subtypes and Development of Hemorrhagic Transformations

<table>
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<tr>
<th></th>
<th>LCS, n=23</th>
<th>Non-LCS, n=70</th>
<th>SPA Infarct, n=13</th>
<th>Non-SPA Infarct, n=75</th>
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<tr>
<td>Any HT</td>
<td>3 (13.0)</td>
<td>19 (27.1)</td>
<td>0*</td>
<td>22* (29.3)</td>
</tr>
<tr>
<td>HI</td>
<td>1 (4.3)</td>
<td>9 (12.9)</td>
<td>0</td>
<td>10 (13.3)</td>
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<td>PH</td>
<td>2 (8.7)</td>
<td>10 (14.3)</td>
<td>0</td>
<td>12 (16.0)</td>
</tr>
<tr>
<td>SICH</td>
<td>0</td>
<td>3 (4.8)</td>
<td>0</td>
<td>3 (4.0)</td>
</tr>
</tbody>
</table>

HI indicates hemorrhagic infarct; HT, hemorrhagic transformation; LCS, lacunar clinical syndrome; PH, parenchymal hematoma; SICH, symptomatic intracerebral hemorrhage; SPA, single penetrator artery.

Values are N of patients (%) if not otherwise indicated.

* \( P < 0.05 \).

![Figure.](image_url) Modified Rankin scale at discharge among 3 patient groups. Group 1, SPA infarcts; group 2, non-SPA infarcts with LCS; and group 3, non-SPA infarcts with non-LCS. SPA, single penetrator artery; LCS, lacunar clinical syndrome.
lytic therapy, both because of the brevity of the clinical evaluation before treatment and because of the requirement that patients have a potentially disabling deficit, resulting in a high frequency of sensory motor and pure motor syndromes and reduced frequency of pure sensory and dysarthria clumsy hand syndromes. The first ECASS trial showed that clinical presentation as lacunar syndrome within a few hours of stroke onset corresponded to lacunar infarcts in less than one-third of patients. In another study among patients with pure motor hemiparesis and sensory motor syndromes evaluated within 12 to 24 hours from stroke onset, only half had lacunar infarcts.

Our study findings accord with those of previous studies that investigated HT rates after intravenous thrombolysis for patients with lacunar clinical syndromes. The rate of any radiological HT in patients with lacunar clinical syndrome in previous studies has ranged from 6.9% to 9.1%, comparable to the rate of 13.0% in the current series. Our findings suggest that the hemorrhages in these patients likely cluster in the subset of patients with lacunar clinical syndrome but actual underlying large artery ischemia. In our study, any radiological HT occurred in 3 of 10 of such patients vs 0 of 13 with genuine SPA territory ischemia.

Several studies have identified volume of ischemically compromised tissue as a critical risk determinant for HT after intravenous thrombolysis. Early ischemic changes on CT were independently associated with an increased risk of symptomatic HT in the 2 NINDS-tPA trials. In a large series, the volume of early CT change, indexed by lower Alberta Stroke Program early CT score, was associated with increased risk of symptomatic ICH in patients treated with intravenous tPA. In an MRI study, the rate of symptomatic ICH increased with increasing diffusion-weighted imaging lesion volume, from 2% with small lesions (<10 mL) to 12% to 16% with lesions >100 mL. Imaging-confirmed SPA infarcts have small lesion volumes no more than 3.75 mL (1.53 = 3.75). However, we do not know whether a lacunar stroke was an independent variable in the reduced hemorrhagic risk after thrombolysis or whether this finding is purely secondary to the small volume of lacunar strokes.

Because the risk of bleeding into an ischemic field varies directly with volume of injured tissue, ischemic lesions confined to SPA are at a low risk for HT. The risk of bleeding outside the ischemic field is low, but not zero, and may be higher in the oldest (age 85 and older) patients, who may have a greater burden of subclinical amyloid angiopathy.

Increasingly in academic and advanced community practice, thrombolytic treatment decisions are made based on using multimodal CT and MRI, permitting direct imaging delineation of the site and size of the ischemic lesion and the presence or absence of a large artery occlusion. Our results suggest that imaging-based recognition of patients harboring SPA infarcts is a better guide than classical lacunar clinical syndromes in identifying patients at very low risk for HT after intravenous lytic therapy.

This study has limitations. The sample size was modest. Confirmation of our findings in larger datasets is desirable. We excluded from analysis patients who underwent endovascular interventions after intravenous thrombolysis. This exclusion was required to avoid attributing to intravenous tPA HT actually related to the endovascular interventions. This exclusion could lead to an underestimation of the rate of HT in non-SPA patients. However, because patients with SPA infarcts are not candidates for endovascular therapy, this exclusion does not affect the SPA patient analysis. We used infarct topography, “distribution in SPA,” as part of the operational definition of single penetrator infarcts. This approach allows the exclusion of lesions that are small and deep but not confined to a standard penetrator field, such as small pontine lesions that cross the midline or juxtaposed thalamic and internal capsule infarcts. However, even with typical penetrator territory infarcts, we cannot rule out that some cases occurred in the distribution of 2 adjacent, very small penetrators, rather than 1 penetrator. The requirement that infarct diameter is not >1.5 cm would be expected to make such occurrences uncommon.

A potential source of bias in adjudicating the presence of HT was that the same post-treatment scans used to ascertain HT were also 1 source of information regarding classifying cases as SPA vs non-SPA. Several factors worked to mitigate this bias, although not completely remove it, including that different sequences on MRI scans are the primary source of information on HT vs infarct topography, a different reader rated the scans independently for SPA vs non-SPA classification than the readers rating for the presence of HT, and that in patients with pretreatment MRI, pretreatment scan assessments of SPA topography assignment concurred with those obtained on post-treatment scans. A related source of potential bias is that if tPA worked to reduce the size of final infarcts, it could have led to some cases of non-SPA ischemia being classified as SPA ischemia. This concern is attenuated by the fact that no such instance was observed in the cases with pretreatment diffusion MR of CT perfusion imaging. However, confirmation in a larger series with multimodal pretreatment imaging is needed. A final limitation is that we could not figure out whether small ischemic lesion volume fully accounts for the lower HT risk of SPA infarcts, or if other factors contribute, because pretreatment diffusion MRI or perfusion CT assessments of ischemia lesion size were not obtained in all cases.

**Conclusion**

In conclusion, HT after lytic therapy in imaging-confirmed SPA infarcts is uncommon. Imaging demonstration of ischemia confined to SPA territory better-identifies this population at low risk for the hemorrhagic complications than classical clinical lacunar syndromes.

**Acknowledgments**

Study concept and design performed by S.J.L., J.L.S., and S.S. Acquisition of data performed by J.L.S., D.S.L., L.A., B.O., D.K., P.V., S.S., M.F., and M.T. Analysis and interpretation of data performed by S.J.L., J.L.S., and S.S. Statistical analysis performed by S.J.L. and J.L.S. Drafting of the manuscript performed by S.J.L. Critical revision of the manuscript for important intellectual content performed by J.L.S., D.S.L., L.A., B.O., D.K., M.F., M.T., P.V., and S.S. The authors thank Jeffrey Gornbein, PhD, for expert statistical consultation.
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Disclosures

J.L.S. is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to CoAxia, Concentric Medical, Talectis, Ferrer, AGA Medical, BrainGate, PhotoThera, and Cygnis (all modest); has received lecture honoraria from Ferrer and Boehringer Ingelheim (modest); received devices for use in an NIH multicenter clinical trial from Concentric Medical (modest); has declined consulting/honoraria monies from Genentech since 2002; has declined serving as a medicolegal expert in tPA litigation since 2002; is a site investigator in multicenter trials sponsored by AGA Medical, Vernalis, Paion, Lundbeck, and Neurobiological Technologies for which the UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH IRIS, CLEAR, and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; administers stroke thrombolytic therapy in his practice (<5% of the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH IRIS, CLEAR, and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH CLEAR and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH CLEAR and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; administers stroke thrombolytic therapy in his practice (<5% of effort); and is funded by NIH-NINDS Awards P50 NS044378 and U01 NS 44364. S.S. is an employee of the University of California, which holds a patent on retriever devices for stroke; has been a site investigator in multicenter trials sponsored by Vernalis, Paion, Lundbeck, and Neurobiological Technologies for which the UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH CLEAR and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH CLEAR and IMS 3 multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; administers stroke thrombolytic therapy in his practice (<5% of effort); has served as a medicolegal expert in acute stroke litigation; and is funded by NIH-NINDS Awards P50 NS044378 and U01 NS 44364. D.S.L. is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to CoAxia (modest) and Concentric Medical (modest). L.A., B.O., D.K., P.V., M.F., M.T., and J.G. are employees of the University of California, which holds a patent on retriever devices for stroke.

References

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**Supplemental on-line table.** Patients’ characteristics and comparison of parameters that affect hemorrhagic transformation

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<td>150 [120, 175]</td>
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<td>LCS</td>
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Initial lab findings

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<td>Diastolic blood pressure, mmHg</td>
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<td>Serum glucose, mg/dL</td>
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<td>109 [99, 140]</td>
<td>112 [103, 132]</td>
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<td>39.2±4.6</td>
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<td>White blood cell, ml</td>
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<td>9,468±2,562</td>
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<tr>
<td>Platelet, x10^3/μL</td>
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<td>229.8±45.5</td>
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<td>0.856</td>
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LCS, lacunar clinical syndrome; SPA, single penetrator artery;

Values are mean±SD or number of patients (%) if not indicated; Values in square brackets represent inte