Thrombolysis Despite Recent Stroke
A Case Series

Mohammed Alhazzaa, FRCP; Mukul Sharma, MD, MSc, FRCP; Dylan Blacquiere, MD, FRCP; Grant Stotts, MD, FRCP; Matthew Hogan, MD, PhD, FRCP; Dar Dowlatshahi, MD, PhD, FRCP

Background and Purpose—Thrombolysis in ischemic stroke is contraindicated in patients who have had a stroke within 3 months. However, it is unclear whether thrombolytic therapy is associated with adverse outcomes in this population. We report the characteristics and outcomes of patients treated with systemic recombinant tissue-type plasminogen activator in the context of known or unknown recent stroke.

Methods—We identified patients who received recombinant tissue-type plasminogen activator despite recent stroke (within 3 months of acute thrombolysis). Clinical and radiological findings were collected, including early neurological worsening and hemorrhagic transformation on unenhanced computed tomography at 24 hours. Clinical outcome measured by modified Rankin Scale was determined at 3 months from onset.

Results—Six patients presenting with acute stroke within 3 months of previous stroke were identified (median age, 76 years; median National Institutes of Health Stroke Scale, 8.5). Hemorrhagic transformation was seen in the follow-up computed tomography scan in 3 of 6 cases: all were hemorrhagic transformation 1 (petechial hemorrhage), asymptomatic, and mostly located within the area of subacute infarction. There was no early neurological deterioration, and 3 patients had modified Rankin Scale ≤ 2 after 3 months.

Conclusions—In our center, we thrombolysed 6 patients despite recent stroke. Three patients had asymptomatic petechial hemorrhagic transformation within the area of subacute infarct, without apparent neurological worsening. Prospective studies are needed to explore the possible safety of tissue-type plasminogen activator in the context of previous subacute stroke in otherwise eligible patients. (Stroke. 2013;44:1736-1738.)

Key Words: outcome ■ recurrent stroke ■ safety ■ silent stroke ■ sICH ■ thrombolysis

A substantial number of patients with acute stroke may be denied thrombolysis because of a recent stroke. This approach is understandable given safety concerns and strict inclusion criteria in the landmark thrombolytic trials. But with increasing thrombolysis experience, there has been active debate on recombinant tissue-type plasminogen activator (rtPA) usage beyond the guidelines because intravenous (IV) rtPA can potentially benefit a wider range of patients who otherwise have no therapeutic options. To date, there have been no prospective studies examining the safety of thrombolysis in patients who have had subacute strokes. In this case series, we examined clinical and radiological outcomes of patients who received IV rtPA thrombolysis despite recent stroke (TDRS).

Methods
We performed a review of prospectively collected data on all consecutive patients presenting to our stroke center between 2008 and 2012 who received IV rtPA therapy for acute stroke, despite previous stroke within 3 months. In these patients, the recent stroke was either unknown to the treating clinician at the time of thrombolysis, or the benefit was felt to outweigh the risks, and IV rtPA was administered after consent. Baseline demographic, laboratory, and imaging findings were collected. Patients underwent routine noncontrast computed tomography at 24 hours after treatment; these were reviewed for evidence of hemorrhagic transformation and graded according to the European Cooperative Acute Stroke Study (ECASS) classification. Symptomatic intracranial hemorrhage was defined as an increase in National Institutes of Health Stroke Scale of ≥4 points within the first 24 hours after thrombolytic therapy, associated with a hemorrhage seen on the follow-up computed tomography scan. Clinical outcome was evaluated using mRS at 3 months.

Results
Between 2008 and 2012, our center thrombolysed an average of 98 patients per year (IV tPA only; 27% thrombolysis rate/y). Of these, 6 patients meeting inclusion criteria were identified. Clinical and radiological characteristics are shown in the Table. Four patients had known recent ischemia, whereas 2 (cases 2 and 3) had recent symptoms that were not known at the time of thrombolysis because of language deficits but had subacute ischemic changes on initial noncontrast computed tomography; a history consistent with subacute stroke was confirmed from family arriving shortly after thrombolysis. Three patients (cases 1, 5, and 6) had been treated with tPA...
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for a stroke within 3 months before treatment for the recurrent stroke. Median age was 76 and median baseline National Institutes of Health Stroke Scale was 8.5. Three patients were >80 years of age. All patients were treated with IV tPA 0.9 mg/kg. None had hemorrhage or extensive damage from the recent ischemia on baseline computed tomography (Figure). The interval between recent and index infarctions was variable, ranging from 6 days to 10 weeks. Hemorrhagic transformation was seen in the 24-hour follow-up computed tomography scan in 3 of 6 cases: all were hemorrhagic transformation 1, asymptomatic, and located in the region of prior infarction (Figure). No patients had symptomatic intracranial hemorrhage or early neurological deterioration at 24 hours. At 3-month follow-up, 3 patients had an mRS of <2. Among the other 3 cases who had mRS of >2, 2 had elevated baseline (pretreatment) mRS.

Discussion

Symptomatic hemorrhage from acute systemic thrombolysis is the major adverse consequence of acute stroke treatment. On the basis of current guidelines,7 rtPA is contraindicated in those with stroke or systemic thrombolysis within 3 months. This contraindication has been adopted from eligibility criteria of the original thrombolysis trials in acute myocardial infarction and ischemic stroke7; although, there is no evidence for worsened outcomes in this group.8 The real biological safety window has not been addressed in stroke trials. Observational studies have reported relative safety with rtPA administration outside established guidelines.3,9 Patients with prior stroke do have favorable outcomes after IV rtPA.10 Yet, there are few data about the safe time frame for IV rtPA administration after a previous infarct. In our study, we reviewed a series of patients who received off-protocol IV rtPA despite subacute infarction. Although we report petechial hemorrhage on 24-hour noncontrast computed tomography in 3 patients, there was no symptomatic intracranial hemorrhage or neurological deterioration after thrombolysis in this case series, which included elderly and repeated thrombolysis patients.

Table. Demographic, Clinical, and Radiological Characteristics of Patients

<table>
<thead>
<tr>
<th>Cases and Characteristics</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Age, y</td>
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<td>28</td>
<td>69</td>
<td>71</td>
<td>83</td>
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<td>AFib, HTN</td>
<td>CAD, HTN, HC, DM, smoking</td>
<td>CAD, smoking</td>
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<tr>
<td>TOAST</td>
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<td>8</td>
<td>8</td>
<td>9</td>
<td>4</td>
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<tr>
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<td>9</td>
<td>9</td>
<td>10</td>
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<tr>
<td>Recent infarct</td>
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<td>Left MCA</td>
<td>Right cerebellum</td>
<td>Right MCA</td>
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<td>2.23</td>
<td>10.5</td>
<td>3.2</td>
<td>2.22</td>
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<td>Interinfarcts interval</td>
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<td>&lt;10 d</td>
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<tr>
<td>HT</td>
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<tr>
<td>3 mo mRS</td>
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</table>

AFib indicates atrial fibrillation; ASPECTS, Alberta Stroke Program Early Computed Tomography score; CAD, coronary artery disease; DM, diabetes mellitus; HC, hypercholesterolemia; HT, hemorrhagic transformation; HTN, hypertension; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.
Pretreatment MRI can potentially identify patients who do not seek medical attention for recent neurological symptoms, and have difficulty conveying them during a subsequent disabling stroke. In 2 retrospective studies, the prevalence of recent silent cerebral ischemia on prethrombolysis MRI is up to 18%; the frequency of symptomatic intracranial hemorrhage in these patients varied between 0% and 5%. Three of our cases had repeat thrombolysis for a recurrent stroke after successful treatment of the initial event, in keeping with 3 previously published cases of repeated systemic thrombolysis within 3 months with no complications. Repeat thrombolysis is an equally controversial relative exclusion that warrants further study.

These observations around administering or repeating thrombolysis in the context of recent infarction are promising but unproven. It is of note that half of our treated cases had petechial hemorrhage in the subacute infarct. Furthermore, our study had a small number of cases that were retrospectively analyzed, and outcome assessment was confounded by premorbid disability. Nevertheless, we present these data to challenge our treatment paradigms and further stimulate discussion around the evidence and relevance of our current IV rtPA exclusion criteria. There may be a subgroup of individuals who may be safely treated within 3 months of a previous stroke. The characteristics of this group await definition.

Disclosures
Dr Dowlatshahi is funded by a research salary award from the Department of Medicine. The other authors have no conflicts to report.

References
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