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Safety Outcomes after Thrombolysis for Acute Ischemic Stroke in Patients with Recent Stroke

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Abstract

Background and Purpose—It is uncertain whether prior ischemic stroke within 3 months of receiving intravenous thrombolysis (IV-tPA) for acute ischemic stroke (AIS) is associated with an increased risk of adverse outcomes.

Methods—Using administrative claims data, we identified adults with AIS who received IV-tPA at California, New York, and Florida hospitals from 2005–2013. Our primary outcome was intracerebral hemorrhage (ICH) and our secondary outcomes were unfavorable discharge disposition and inpatient mortality. We used logistic regression to compare rates of outcomes in patients with and without previous ischemic stroke within 3 months of IV-tPA for AIS.

Results—We identified 36,599 AIS patients treated with IV-tPA, of whom 568 (1.6%) had a prior ischemic stroke in the past 3 months. Of all patients who received IV-tPA, the rate of ICH was 4.9% (95% CI, 4.7–5.1%), and death occurred in 10.7% (95% CI, 10.4–11.0%). After adjusting for demographics, vascular risk factors, and the Elixhauser comorbidity index, previous ischemic stroke within 3 months of thrombolysis for AIS was not associated with an increased risk of ICH (OR, 0.9; 95% CI, 0.6–1.4; P=0.62), but was associated with an increased risk of death (OR 1.5; 95% CI, 1.2–1.9; P=0.001) and unfavorable discharge disposition (OR 1.3; 95% CI, 1.0–1.7; P=0.04).

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Disclosures

None.

Conclusions—Among patients who receive IV-tPA for AIS, recent ischemic stroke is not associated with an increased risk of ICH but is associated with a higher risk of death and unfavorable discharge disposition.

Indexing terms

Stroke; Intracerebral Hemorrhage; Ischemic Stroke

Subject codes

Intracranial Hemorrhage; Ischemic Stroke; Mortality/Survival

While the updated Food and Drug Administration (FDA) label no longer considers recent stroke to be a contraindication to intravenous tissue plasminogen activator (IV-tPA) use, the American Heart Association/American Stroke Association (AHA/ASA) continues to recommend against IV-tPA use in acute ischemic stroke (AIS) patients with a history of stroke within the previous 3 months.[1, 2] An enhanced understanding of the risk of thrombolysis in patients with AIS with recent stroke is crucial as approximately 20% of ischemic strokes are recurrences and up to 20% of these recurrences occur within 3 months of the initial event.[3, 4] Therefore, we evaluated whether a history of ischemic stroke within the previous 3 months of thrombolysis for AIS is associated with a heightened risk of intracerebral hemorrhage (ICH), unfavorable discharge disposition, or death in a large, heterogeneous group of patients.

Methods

Design

We performed a retrospective cohort study of AIS patients treated with IV-tPA using publically available data from the Agency of Healthcare Research and Quality, extracted from administrative claims from California, New York, and Florida (\Supplemental Methods). The Weill Cornell Medicine institutional review board approved our analysis of these data.

Patients

We included adults with AIS treated for the first time with IV-tPA between 2005 and 2011 in California, 2005 and 2013 in Florida, and 2006 and 2013 in New York. We defined AIS using *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes 433.×1, 434.×1, or 436 in any diagnosis code position in the absence of a primary discharge code for rehabilitation (V57) or any codes for subarachnoid hemorrhage (430), or trauma (800–804, 850–854). Use of IV-tPA was defined by the *ICD-9-CM* procedure code (99.10) in any procedure code position.

Measurements

Our exposure variable was a prior ischemic stroke within 3 months of IV-tPA for AIS. For every case, we identified the presence or absence of a separate hospitalization for ischemic stroke in the 3 months before thrombolysis for AIS. The primary outcome was the

development of ICH within the index visit for AIS during which the patient received IV-tPA. ICH was defined by the presence of the *ICD-9-CM* code 431 in any diagnosis position in the absence of a present on admission *ICD-9-CM* code for ICH. Secondary outcomes were inpatient mortality and unfavorable discharge disposition. Discharge disposition has been shown to correlate with 90-day and 1-year functional outcomes based on the modified Rankin Scale.[5] Discharge disposition was categorized as either unfavorable (discharge to skilled nursing facility, subacute care center, chronic rehabilitation center, hospice, or death) or favorable (discharged home), as in prior analyses.[5]

Statistical Analysis

Descriptive statistics were used to calculate crude rates of patient characteristics and outcomes. Multivariable logistic regression was used to examine the association between recent prior ischemic stroke and our outcomes of interest while adjusting for potential confounders: demographics, stroke risk factors (Supplemental Methods), and the Elixhauser Comorbidity Index. As our goal was to isolate the relationship between exposures and outcomes, all variables were left in the model regardless of statistical significance. In a prespecified secondary analysis, we divided the 3-month time period before IV-tPA administration into 1-month intervals to determine whether the length of time between prior stroke and thrombolysis for AIS modifies the risk of outcomes. We performed four sensitivity analyses to test the validity of our results (Supplemental Methods). In a post-hoc exploratory analysis, we assessed the risk of ICH, death, and unfavorable discharge disposition in patients with claims for AIS not treated with IV tPA stratified by history of ischemic stroke hospitalization in the past 3 months. Statistical significance was set at α=0.05.

Results

Patient Characteristics

We identified 36,599 patients who were treated with IV-tPA for AIS, among whom mechanical thrombectomy was performed in 2,093 (5.7%). History of ischemic stroke within 3 months was present in 568 cases (1.6%). Patients with previous stroke were younger (mean age, 69.0 [±14.1] vs. 70.9 [±14.6] years), more likely to have peripheral vascular disease, and had more Elixhauser comorbidities (3.4 vs. 3.2, P=0.01) (Supplemental Table I).

Main Analyses

The primary outcome of post-thrombolysis ICH occurred in 1,792 (4.9%; 95% Confidence Interval [CI], 4.7–5.1%) patients, including 24 (4.2%; 95% CI, 2.6–5.9%) patients with recent prior ischemic stroke and 1,768 (4.9%; 95% CI, 4.7–5.1%) patients without. Patients with ICH were older (mean age, 74.6 [±12.4] vs. 70.7 [±14.6] years) and more likely to have medical comorbidities (Supplemental Table II). In-hospital death occurred in 10.7% (95% CI, 10.4–11.0%) of all AIS patients, including 84 (14.8%; 95% CI, 11.9–17.7%) patients with recent prior stroke and 3,839 (10.6%; 95% CI, 10.3–11.0%) patients without. Among the 34,715 (94.9%) patients with available discharge disposition data, unfavorable discharge disposition occurred in 73.4% (95% CI, 72.9–73.9%) of patients, including 349 (78.3%;

95% CI, 74.4–82.1%) patients with recent prior stroke and 25,139 (73.4%; 95% CI, 72.9–73.8%) patients without.

After adjusting for demographics, stroke risk factors, and the Elixhauser comorbidity index, a previous ischemic stroke within 3 months of thrombolysis for AIS was not associated with an increased risk of ICH (odds ratio [OR] 0.9; 95% CI, 0.6–1.4; P=0.62), but was associated with an increased risk of death (OR 1.5; 95% CI, 1.2–1.9; P=0.001) and unfavorable discharge disposition (OR 1.3; 95% CI, 1.0–1.7; P=0.04). The risk of ICH in patients with a recent ischemic stroke was unchanged in four sensitivity analyses (Supplemental Results). In secondary analysis, ICH risk did not vary when stratified by 1-month time intervals from the time of prior stroke (Supplemental Table III).

Post-hoc Analysis

Recent ischemic stroke in patients with claims for AIS who did not receive IV-tPA was not associated with an increased risk of ICH (OR 1.0; 95% CI, 0.8–1.2, P=0.86), but was associated with an increased risk of death (OR 2.1; 95% CI, 2.0–2.2, P <0.001) and unfavorable discharge disposition (OR 1.4; 95% CI, 1.3–1.4, P <0.001) (Supplemental Table IV).

Discussion

In a large, heterogeneous sample of patients with AIS treated with IV-tPA, history of recent stroke was not associated with an increased risk of ICH, but was associated with an increased risk of inpatient death and unfavorable discharge disposition. These findings are consistent with and build upon those reported in previous, smaller studies.[6, 7] The higher risk of death and unfavorable discharge disposition may be due to recurrent strokes generally being more severe and disabling, as well as more limitations of care in patients that have a second stroke. Furthermore, in an exploratory analysis in patients with claims for AIS not treated with IV-tPA, recent ischemic stroke remained associated with an increased risk of unfavorable discharge disposition and inpatient death, suggesting that recurrent ischemic stroke rather than treatment with IV-tPA portends poor outcome.

This study has several limitations. First, data on stroke severity, size, location, onset-to-treatment time, and patients' baseline neurological status were unavailable. Second, patients who received IV-tPA despite a recent historical stroke may have been a closely-selected, lower risk population as practitioners administered IV-tPA in light of the AHA/ASA recommendation to not administer IV-tPA to such patients. Third, since we restricted our cohort to patients with AIS treated with IV-tPA for the first time, our results may not generalize to patients with prior IV-tPA use. Fourth, we lacked data on long-term functional outcomes, which are typically used to evaluate the effect of stroke interventions in randomized trials. Fifth, our use of administrative data may have led to a misclassification of stroke or ICH events and we lacked a well-validated algorithm to identify recurrent ischemic stroke, particularly for cases not treated with IV-tPA as in our post-hoc exploratory analysis. In addition, there is no specific *ICD-9-CM* code for hemorrhagic conversion after IV-tPA for AIS. We aimed to increase our accuracy by including only those patients who had *ICD-9-CM* codes for ICH (not present on admission), AIS, and IV-tPA during the same

hospitalization. Nonetheless, some ICHs may have occurred later in the AIS hospitalization and therefore might not have been a direct consequence of IV-tPA, although this would be expected to occur with similar frequency in patients with and without recent prior stroke. Lastly, we lack data on whether the ICH was symptomatic or asymptomatic.

Our results, in conjunction with previously published studies, suggest that select use of IV-tPA in patients with previous ischemic stroke in the past 3 months is not associated with an increased risk of ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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