Thrombolytic Treatment of Patients With Acute Ischemic Stroke Related to Underlying Arterial Dissection in the United States

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Objective: To determine the outcomes related to thrombolytic treatment of an acute ischemic stroke secondary to an arterial dissection in a large national cohort.

Design: Retrospective database study.

Setting: Nationwide Inpatient Sample data files from 2005 to 2008.

Patients: We determined the frequency of underlying arterial dissection among patients with acute ischemic stroke treated with thrombolytic treatment and associated in-hospital outcomes.

Main Outcome Measures: All the in-hospital outcomes were analyzed after adjusting for potential confounders using multivariate analysis.

Results: Of the 47,899 patients with ischemic stroke who received thrombolytic treatment, 488 (1%) had an underlying dissection. The intracranial hemorrhage rates did not differ between patients with ischemic stroke with or without underlying dissection who received thrombolytic treatment (6.9% vs 6.4%). After adjusting for age, sex, hypertension, diabetes mellitus, renal failure, congestive heart failure, and hospital teaching status, presence of dissection was associated with higher rates of moderate disability (odds ratio, 2.8; 95% confidence interval, 1.7-4.6; P < .001) at discharge. The interaction terms between dissection and thrombolytic treatment among all patients with ischemic stroke for predicting in-hospital mortality (P = .84) and minimal disability (P = .13) were not statistically significant.

Conclusions: The adjusted rate of favorable outcomes is lower among patients with ischemic stroke with underlying arterial dissection following thrombolytic treatment compared with those without underlying dissections. However, the observed lower rates are not influenced by thrombolytic treatment.

thors consider the lysis and regression of mural thrombus to be beneficial for vessel flow improvement.7 The current American Stroke Association Stroke Council–American Heart Association guidelines recommend avoiding any anticoagulation or antiplatelet agents in the first 24 hours after thrombolysis to reduce the risk of post-thrombolytic intracerebral hemorrhage.1 Most physicians consider short-term anticoagulation or antiplatelet treatment as appropriate treatment in such patients to reduce thromboembolic events and progression of ischemic deficits.8 In patients with arterial dissection, avoidance of these agents in the period of maximum vulnerability for recurrent ischemic events may adversely affect the outcome of patients with underlying dissection. We performed this study because, to our knowledge, there is no large study that has reported the results of thrombolytic treatment in this patient population with unique risk-benefit attributes.

**METHODS**

We used the data from the Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality.9-11 Briefly, the NIS is the largest all-payer inpatient care database in the United States focusing on identification, tracking, and analyzing national trends in health care use, access, charges, quality, and outcomes based on data derived from approximately 20% stratified sample of US community hospitals, approximately 5 to 8 million hospital stays and all discharge data from approximately 1000 hospitals. The NIS data available for 2005 through 2008 were used, analyzing inpatient records including clinical and resource use information derived from discharge abstracts. The data comprise more than 100 clinical and nonclinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patients’ admission and discharge status, and patient demographic information (eg, sex, age, race/ethnicity, expected payment source, total charges, and length of stay). To facilitate production of national estimates, the NIS provides both hospital and discharge weights. Detailed information on the design of the NIS is available at http://www.hcup-us.ahrq.gov.

We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary diagnosis codes 433, 434, 436, 437.0, and 437.1 to identify the patients admitted with ischemic stroke. Patients who underwent thrombolytic treatment were identified by procedure code 99.10. In 1998, a new procedure code, 99.10, was designated for injection or infusion of thrombolytic agents, permitting estimation of national and statewide use.12,13 Patients with dissection were identified using ICD-9-CM codes 433.2, 433.21, and 433.24 as any of the 15 secondary discharge diagnoses in patient records. Cardiovascular risk factor information was obtained from the Agency for Healthcare Research and Quality comorbidity data collected for each patient. The ICD-9-CM secondary diagnosis codes were used to identify those with stroke-associated complications such as pneumonia (486, 481, 482.8, and 482.3), urinary tract infection (599.0 and 590.9), sepsis (995.91, 996.64, 038, 995.02, and 999.3), deep venous thrombosis (451.1, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, and 453.9), pulmonary embolism (415.1), intracerebral or subarachnoid hemorrhage (430, 431, and 432), and acute myocardial infarction (410). We also used ICD-9-CM procedure codes to estimate the percentage of stroke patients who underwent stroke-related procedures such as cerebral angiography (88.41), carotid angioplasty/stent placement (00.63/00.64), intracranial angioplasty/stent placement (00.62/00.65), gastrostomy (43.11/43.19), tracheostomy (31.10, 31.20, 31.21, or 31.29), and carotid endarterectomy (38.12) and those who had postprocedure stroke (997.02). Mechanical thrombectomy and/or intra-arterial thrombolytic administration was identified using diagnosis-related group codes 23, 24, or 543 or ICD-9-CM procedure codes 00.41 to 00.43 or 39.74. Posterior circulation dissections were identified by ICD-9-CM codes 433.01 and 433.2 for stenosis/occlusion involving the basilar or vertebral arteries. All other dissections were classified as anterior circulation dissections. Indeterminate location was used if none of the arterial location codes were used.

We ascertained patients’ age, sex, race/ethnicity, length of stay, discharge status (categorized into routine, home health care, short-term hospital, other facility including intermediate care and skilled nursing home, or death), medical complications, procedures performed, and total hospitalization charges for patients who underwent thrombolytic treatment in strata based on presence or absence of underlying dissection. We categorized routine discharge as minimal disability and any other discharge status as moderate to severe disability. The statistical analyses were performed based on these weighted numbers and incorporated the complex sampling of the NIS, following Healthcare Cost and Utilization Project recommendations.14 We used the χ2 test for categorical data and analysis of variance for continuous data to detect any significant differences in variables among patients with and without arterial dissection and ischemic stroke treated with thrombolysis. We adjusted for multiple comparisons using Bonferroni correction. We also evaluated the proportion of patients in the two groups admitted to the various types of hospitals (rural, urban, nonteaching, and urban teaching hospitals).

We used SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) to convert raw counts generated from the NIS database into weighted counts that we used to generate national estimates. All analyses accounted for the complex sampling design and sample discharge weights of the NIS, following Healthcare Cost and Utilization Project–NIS recommendations (Healthcare Cost and Utilization Project methods series report 2003-2002). We performed univariate analysis with the χ2 test for categorical and the t test for continuous variables to identify differences in study variables and end points between the two patient groups. A logistic regression analysis was used to identify the association between presence of dissection and odds of (1) minimal disability, (2) moderate to severe disability, and (3) death. We adjusted for age and sex in the initial models and subsequently adjusted for all the variables that were different between patients with or without dissections in the univariate analysis.

We also analyzed the data from patients with acute ischemic stroke from the NIS who did not receive any thrombolysis to evaluate whether the differences in study outcomes between patients with or without dissection were only seen in patients who underwent thrombolytic treatment or were also seen among non–thrombolytic-treated patients. We performed logistic regression analysis to identify the association between the presence of dissection and odds of (1) minimal disability, (2) moderate to severe disability, and (3) death, in a manner similar to the earlier-mentioned paradigm. We further tested the interaction between dissection and thrombolytic treatment. A logistic regression analysis was performed including all patients with a primary diagnosis of ischemic stroke irrespective of presence of dissection and thrombolytic treatment. The interaction term was added to the multivariate model that included dissection and thrombolytic treatment as predictor variables after adjusting for the earlier-mentioned confounders with the dependant variables of (1) minimal disability, (2) moderate to severe disability, and (3) death.
To validate the method of ascertainment of arterial dissection in the NIS database and the accuracy of ICD-9-CM code (443.2, 443.21, and 443.24), we compared the ICD-9-CM codes assigned to patients with ischemic stroke and dissection identified from a detailed medical record review of ischemic stroke admissions at 2 university-affiliated tertiary care hospitals in Minneapolis, Minnesota. The positive predictive value was 82.1% for the ICD-9-CM codes for dissection among 134 patients with ischemic stroke and dissection.

RESULTS

Of the 47,899 patients with ischemic stroke who received thrombolytic treatment, 488 (1%) had an underlying dissection. The location of dissection was classified as anterior circulation in 25%, posterior circulation in 10%, and indeterminate in 65%. The mean age of the patients was significantly lower in patients treated with thrombolysis who had underlying dissection compared with those without a dissection (Table 1). The proportion of women was lower among patients treated with thrombolysis who had an underlying dissection. There was also a difference in the race/ethnicity of patients in the 2 groups: the proportion of African American patients was lower and that of white and Hispanic patients was higher among patients treated with thrombolysis who had an underlying dissection. The proportions of patients with hypertension, diabetes mellitus, congestive heart failure, or renal failure were lower in patients treated with thrombolysis who had an underlying dissection. There was a higher rate of admission to large hospitals, based on number of beds, in the group of patients treated with thrombolysis who had an underlying dissection.

The rate of myocardial infarction was significantly lower among patients treated with thrombolysis who had an underlying dissection. The rate of intracerebral and subarachnoid hemorrhages were similar among patients treated with thrombolysis with or without an underlying dissection. There were no differences in the rates of other complications between the 2 groups, including in-hospital pneumonia and urinary tract infection (Table 1). The rate of mechanical thrombectomy and/or intra-arterial thrombolytic administration was significantly higher among patients with ischemic stroke with underlying dissection. There was a significantly higher rate of cerebral angiography and carotid angioplasty/stent placement in patients treated with thrombolysis who had underlying dissection compared with those without underlying dissection. There appeared to be a 2-fold higher rate of intracranial angioplasty/stent placement among patients treated with thrombolysis who had underlying dissection. Postprocedural stroke (used as a surrogate for procedure-related dissection) was seen in 1.5% of the patients with underlying dissections treated with thrombolysis.

A comparison between patients with underlying arterial dissections who did or did not receive intravenous thrombolysis (Table 1) suggested that patients who received thrombolysis had a higher rate of medical comorbidities, adjunctive procedures, and medical complications and lower rates of minimal disability. A similar pattern was seen among patients with ischemic stroke without underlying dissections.

The mean length of stay in patients without underlying dissection was 7.19 days (95% confidence interval [CI], 6.9-7.4 days) vs 7.87 days (95% CI, 6.5-9.3 days) in patients with underlying dissection (P = .38) (Table 1). The in-hospital mortality rate was similar between the 2 groups (10.66% vs 11.22%; P = .5). The mean hospital charges were $62,431 in patients without underlying dissection vs $101,203 in patients with underlying dissection (P < .001). After adjusting for age and sex, presence of dissection was associated with higher rates of moderate to severe disability (odds ratio [OR], 2.6; 95% CI, 1.6-4.3). After adjusting for age, sex, hypertension, diabetes mellitus, renal failure, congestive heart failure, and hospital teaching status, presence of dissection was associated with higher rates of moderate to severe disability (OR, 2.8; 95% CI, 1.7-4.6; P < .001) (Table 2). There appeared to be a higher in-hospital mortality among patients with dissection who received thrombolytic treatment.

We also analyzed the data for patients with ischemic stroke who did not receive thrombolytic treatment and found that patients with arterial dissection had higher rates of inpatient mortality and discharge to nursing facilities as well as lower rates of discharge to home. When adjusted for age, sex, hypertension, diabetes mellitus, renal failure, congestive heart failure, and hospital teaching status, the odds of in-hospital mortality were higher among patients with dissection (OR, 2.7; 95% CI, 1.9-3.8) (P = .001) and higher for rates of moderate to severe disability (OR, 3.5; 95% CI, 3.1-3.9) (P = .001). The interaction terms between dissection and thrombolytic treatment among all patients with ischemic stroke for predicting in-hospital mortality (P = .78) and minimal disability (P = .95) were not significant.

COMMENT

Our results suggest that the adjusted rate of moderate to severe disability (a surrogate for unfavorable outcomes) is higher among patients with ischemic stroke with underlying dissection following thrombolytic treatment compared with those without underlying dissections. The observation confirms the results derived from an analysis of patients with ischemic stroke receiving intravenous thrombolysis among 9 stroke centers in Switzerland. The confirmation of such findings in a large (approximately 50,000 patients treated with intravenous thrombolysis), diverse, and nationally representative study sample provides additional evidence regarding the generalization of these findings. Because our study also included patients with dissections not treated with intravenous thrombolysis, we were able to demonstrate that the higher rate of moderate to severe disability among patients with ischemic stroke with underlying dissection is not unique to the thrombolytic-treated group but is also seen in patients who are not treated with thrombolysis. The lack of any demonstrable interaction in the multivariate model or excessive rates of postthrombolytic hemorrhages also confirm that the use of thrombolytic treatment (among thrombolytic-treated patients with underlying dissection) was not an independent factor in determining outcomes in patients with dissection.
Our results point out the increased vulnerability of patients with dissection to lower rates of favorable outcomes despite thrombolytic treatment. The observation is similar to a study of 1062 patients with ischemic stroke treated with intravenous thrombolysis, of whom 55 had underlying cervical artery dissection. The rates of favorable outcomes were lower (36% vs 44%) among patients treated with thrombolytics compared with those without underlying cervical artery dissection. The lower odds of favorable outcomes were seen even after adjustment for age, sex, and National Institutes of Health Stroke Scale (NIHSS) score. The rates of intracerebral hemorrhage were similar in the 2 groups. Another review of 30 patients confirmed the high rate of poor outcomes, reporting that 53% of the patients with ischemic stroke related to dissections treated with either intravenous or intra-arterial thrombolysis died or had disability. In another report of 33 patients with acute ischemic stroke associ-
ated with carotid artery dissection, 48% died or had disabili
ty despite treatment with intravenous thrombolysis. The underly-
ing mechanism for lower rates of favorable outcome could be a higher rate of flow-
limiting nonthrombotic lesions or a higher level of plate-
let activation and aggregation resulting in platelet-rich thromboembolisms, which are less amenable to throm-
bolitics. The high rate of cervical internal carotid artery occlu-
sions and associated suprachinoid internal carotid artery (tandem) occlusions seen in patients with underly-
ing dissection may account for the relative lack of benef-
it with intravenous thrombolysis. Both factors have been
associated with relatively poor response to intravenous thromboly-
sis in previous studies.8 Exploration of stent placement in com-

Table 2. Multivariate Analyses Evaluating the Effect of Underlying Arterial Dissections on Various Discharge Outcomes in Thrombolytic- and Non–Thrombolytic-Treated Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
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<tr>
<td></td>
<td>Value</td>
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<tr>
<td></td>
<td>Thrombolytic-Treated Patients With Thrombolytic Stroke</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Minimal disability</td>
<td>1.0 [Reference]</td>
<td>1.0 [Reference]</td>
</tr>
<tr>
<td>Moderate to severe disability</td>
<td>1.4 (0.8-2.3)</td>
<td>.17</td>
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<tr>
<td>In-hospital mortality</td>
<td>1.3 (0.8-2.6)</td>
<td>.43</td>
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<tr>
<td></td>
<td>Non–Thrombolytic-Treated Patients With Thrombolytic Stroke</td>
<td>Adjusted</td>
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<tr>
<td>Minimal disability</td>
<td>1.0 [Reference]</td>
<td>1.0 [Reference]</td>
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<tr>
<td>Moderate to severe disability</td>
<td>1.3 (1.1-1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1.0 (0.7-1.4)</td>
<td>.94</td>
</tr>
</tbody>
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Abbreviation: CI, confidence interval; OR, odds ratio.
<sup>a</sup>Adjusted for age and sex.
<sup>b</sup>Adjusted for age, sex, hypertension, diabetes mellitus, renal failure, congestive heart failure, and hospital teaching status.

sible for death in 5% of the patients and no procedural complications or new dissections were observed in any of the patients.

We did not find any increase in the principal safety end point of postthrombolytic intracranial hemorrhage with dissections, similar to other studies; therefore, the use of thrombolytics in this patient population does not need to be discontinued based on safety concerns. The results argue for additional treatment modalities after thrombolytic treatment in patients with underlying dissection to reduce the rate of poor outcomes. The scenario is analogous with differential outcomes seen in patients with an NIHSS score of 10 or greater and those with a score of less than 10 following thrombolytic treatment. A similar difference in outcomes has been reported for patients with a hyperdense middle cerebral artery sign. These observations have led to the evaluation and use of endovascular treatment following intravenous thrombolytic treatment in patients with an NIHSS score of 10 or greater or those with a hyperdense middle cerebral artery sign. Patients with dissection may be treated with a similar paradigm if computed tomographic or magnetic resonance angiography or magnetic resonance T1 fat-saturated sequences before or after intravenous thrombolytic treatment suggest arterial dissection; follow-up angiography and additional endovascular treatment may be considered. Stent placement for restoring patency of the true lumen and mechanically occluding the false lumen has shown potential in vascular occlusions associated with dissections. According to American Heart Association–American Stroke Association Stroke Council guidelines, stent placement is an option in symptomatic patients refractory to medical management. Exploration of stent placement in combination with or alternate to intravenous thrombolysis in patients with acute ischemic stroke to recanalize occlusions related to dissections through prospective studies appears to be the next logical step.

We used a large sample size from the NIS data set, which has been used in previous stroke studies with a standardized design to provide a representative esti-
mate of the total hospitalizations within the United States. The database provides minimal details on the severity of neurological deficits, diagnostic study results, and use of procedures. The NIS data also depend on the accuracy of diagnoses and procedures listed on discharge summaries and on the data collection system. We used primary ICD-9-CM codes for identifying patients with ischemic stroke, which has a true positive rate of up to 84% in previous population-based studies. In a study, the sensitivity and specificity of ICD-9-CM procedure code 99.10 for use of thrombolysis in ischemic stroke in comparison with a concurrent prospective registry were 55% and 98%. The high specificity of both codes suggests that the patient designation for each category is most likely accurate, although the exact prevalence may be underestimated. We found a positive predictive value of 82.1% for ICD-9-CM codes for dissection, which supports the accuracy of diagnosis of dissection in our analysis. While such an observation supports the accuracy of ascertainment of cases of dissection, further characterization into anterior and posterior circulation locations is not possible using a rigorous criterion. In an exploratory analysis, only a minority of dissections were located in the posterior circulation among those patients in whom location was specified. Therefore, our study is predominantly a representation of anterior circulation and cervical internal carotid artery dissections, similar to other studies. One study reported that the internal carotid artery, vertebral artery, and both were involved in 75%, 18%, and 7%, respectively, of 200 consecutive patients admitted with cervical dissections at Mayo Clinic. Carotid artery dissections are more likely to present with ischemic stroke and therefore even have a higher prevalence in patients with ischemic stroke. In another analysis, intracranial and/or vertebral artery dissections composed approximately 5% of all patients with dissections. The information does not allow us to ascertain with certainty whether dissection caused the stroke or was an unrelated finding; we cannot differentiate dissections related to procedures such as angiography or angioplasty/stent placement from spontaneous dissections. However, as mentioned earlier, the rare nature of periprocedural events is unlikely to confound the analysis. The discharge functional outcome cannot be measured with the available data, and the closest index is the destination of discharge. Previous studies among patients with ischemic stroke receiving intravenous thrombolysis have suggested that discharge destination correlates with severity of neurological deficits and thrombolytic-related complications. The conclusions regarding disability incurred with ischemic stroke in this analysis need to be interpreted with this understanding.

Our results highlight the importance of developing new strategies to reduce the rate of death and disability among patients with ischemic stroke with underlying dissection following thrombolytic treatment.

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