Thrombolysis for Ischemic Stroke in Children
Data From the Nationwide Inpatient Sample

Nazli Janjua, MD; Abu Nasar, MS; John K. Lynch, DO, MPH; Adnan I. Qureshi, MD

Background and Purpose—Few pediatric reports of thrombolysis exist. We sought to determine national rates of thrombolysis among pediatric ischemic stroke patients using a national database.

Methods—Patients between the ages of 1 and 17 years, entered in the Nationwide Inpatient Sample between 2000 and 2003, with International Classification of Diseases codes for ischemic stroke were included in the study. Differences in mean age, gender distribution, ethnicity, secondary diagnoses, medical complications, associated procedure rates, modes of discharge, and hospital costs between pediatric stroke patients receiving and not receiving thrombolysis were estimated.

Results—In the United States, between 2000 and 2003 an estimated 2904 children were admitted with ischemic stroke, of which 46 children (1.6%) received thrombolytic therapy. Children who received thrombolysis were on the average older (11 versus 9 years), more likely to be male (100% versus 53.8%), with significantly higher hospital costs ($81 800 versus $38 700). These children were also less likely to be discharged home with higher rates of death and dependency, although differences in clinical severity between the 2 groups was not known.

Conclusion—Thrombolysis, though not indicated for patients <18 years of age, is currently being administered to children, with unclear benefit. Larger studies are needed to evaluate the safety and efficacy of this treatment for children. (Stroke. 2007;38:1850-1854.)

Key Words: ischemic ■ pediatric ■ stroke ■ thrombolysis

Ischemic stroke in children between the ages of 30 days and 18 years occurs at a rate of 2 to 3/100 000.1,2 Though this rate is much lower than that seen in the adult population, the sequelae are significant.3 At present, there is minimal epidemiological evidence to guide the treatment of ischemic stroke in the pediatric population. Most acute intervention studies of stroke have excluded children, and treatment decisions are typically based on adult studies, animal studies, or nonrandomized trials. Thrombolytic therapies have been shown to be safe and effective in adults, but there is no data in the population below 18 years of age. There are several reports of intravenous and intra-arterial thrombolysis among children,3-11 but national estimates are unknown. We sought to determine rates of thrombolysis for pediatric ischemic stroke as well as associated demographic and clinical data, and compare these between children who did and did not receive thrombolysis in a national government sponsored database.

Materials and Methods

Nationwide Inpatient Sample

Data were obtained from the Nationwide Inpatient Sample (NIS), developed as part of the Healthcare Cost and Utilization Project (HCUP), a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ), which obtains information from 995 hospitals (7 to 8 million admissions) annually from the HCUP State Inpatient Database (SID), providing a 20% stratified sample of acute care community hospitals.12 Because of hospital reporting differences across geographical regions in the United States, the NIS sampling frame contains 97.6% of the population in the Northeast, 89.6% in the Midwest, 83.7% in the West, and 81.2% in the South. Overall, the NIS sampling frame comprises 73.8% of all United States hospitals and covers 86.8% of the United States population. Inpatient records in the NIS include clinical and resource use information available from discharge abstracts. To allow extrapolation for national estimates, both hospital and discharge weights are provided. Detailed information on the design of the NIS is available at http://www.hcup-us.ahrq.gov. The NIS includes >100 clinical and nonclinical variables for each hospital stay. These include primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographics (eg, gender, age, and race), total charges, and lengths of stay.

Patient Selection and Variables Collected

Patients between the ages of 1 and 17 years, registered in the NIS from the years 2000 to 2003, were included in the analysis. Those with ischemic stroke were identified using the first listed International Classification of Disease, 9th Revision clinical modifier (ICD-9 CM) codes 433, 434, 436, 437.0, 437.1, 437.4, 437.5, 437.7, and 437.8.
### TABLE 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total Pediatric Stroke Patients (n=2904)</th>
<th>Patients Who Received Thrombolysis (n=46)</th>
<th>Patients Who Did Not Receive Thrombolysis (n=2858)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years ±SD)</td>
<td>9.4 ± 5.2</td>
<td>11.1 ± 4.1</td>
<td>9.4 ± 5.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1584 (54.5%)</td>
<td>46 (100.0%)</td>
<td>1538 (53.8%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Female</td>
<td>1320 (45.5%)</td>
<td>0 (0.0%)</td>
<td>1320 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1136 (39.2%)</td>
<td>26 (56.5%)</td>
<td>1110 (39.0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Black</td>
<td>524 (18.0%)</td>
<td>&lt;10 (10.9%)</td>
<td>519 (18.2%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Other/not stated</td>
<td>1244 (42.8%)</td>
<td>15 (32.6%)</td>
<td>1229 (43.0%)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Medical comorbidities/complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moyamoya disease</td>
<td>97 (3.3%)</td>
<td>0 (0.0%)</td>
<td>97 (3.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>182 (6.3%)</td>
<td>0 (0.0%)</td>
<td>182 (6.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiac valvular disease</td>
<td>≤10 (0.3%)</td>
<td>0 (0.0%)</td>
<td>&lt;10 (0.3%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mechanical valves</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Procoaguable conditions</td>
<td>&lt;10 (0.1%)</td>
<td>0 (0.0%)</td>
<td>&lt;10 (0.1%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>23 (0.8%)</td>
<td>0 (0.0%)</td>
<td>23 (0.8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>&lt;10 (0.2%)</td>
<td>0 (0.0%)</td>
<td>&lt;10 (0.2%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>50 (1.7%)</td>
<td>≤10 (10.9%)</td>
<td>45 (1.6%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>89 (3.1%)</td>
<td>0 (0.0%)</td>
<td>89 (3.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>≤10 (0.7%)</td>
<td>≤10 (10.9%)</td>
<td>15 (0.5%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>210 (7.2%)</td>
<td>20 (43.5%)</td>
<td>190 (6.6%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cerebral angiography</td>
<td>817 (28.1%)</td>
<td>24 (52.2%)</td>
<td>793 (27.7%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mode of thrombolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>22 (&lt;1%)</td>
<td>24 (52.2%)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>19 (&lt;1%)</td>
<td>19 (41.3%)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

IV indicates intravenous; IA, intraarterial.

Bold indicates statistically significant comparison.

437.9. The ICD-9 CM procedure code 99.10 was then applied to identify the subpopulation receiving thrombolysis. Age, gender, race, ethnicity, and associated diagnoses (including cardiac, arteriopathic, and hematological), complications, procedures, discharge status, and hospitalization costs were determined for all cases. No variables for stroke severity at baseline were available in the NIS dataset.

**Statistical Analysis**

Comparisons were made between children who received thrombolytic therapy and those who did not. χ² tests and Student t tests were performed to compare differences in the weighted variables between these 2 groups of children, assuming statistical significance at P<0.05. For calculation of average hospital costs, the mean yearly charges for each group were adjusted for the inflation rate in 2005 using an internet tool available at http://www.westegg.com/inflation/ and then averaged for a single average hospital cost for each group. The software program SUDAAN (Research Triangle Inst) was used to convert raw counts generated from the NIS database into weighted counts, representing national estimates. Weighted data were used for all statistical analysis. The study was exempted from formal review by the Institutional Review Board.

**Results**

Demographic and clinical results are tabulated in Table 1 and are summarized below. From 2000 to 2003 there were an estimated 2904 pediatric ischemic stroke admissions, 46 (1.6%) of whom received thrombolytic therapy. Among these patients, the mean age was 11.1 ± 4.1 years versus 9.4 ± 5.2 years among children who did not receive thrombolysis (P=0.22). All 46 children in the NIS receiving thrombolysis were male, compared with 1538 (53.8%) of the other group (P<0.05). Children who received thrombolysis were most often white (56.5%) as compared with other children (39.0%, P=0.32).

None of the children receiving thrombolysis had an associated medical condition commonly reported in children with stroke, whereas among other children, there was a 3.4% rate of moyamoya disease (n=97), a 6.4% rate of sickle cell disease (n=182), a 0.3% rate of cardiac valvulopathy (n=10), and a 0.1% rate of procoaguable conditions (n=10). There were few reported complications including deep venous thrombosis and pneumonia (n=10, 10.9%) and no cases of myocardial infarction, pulmonary embolism, intracranial hemorrhage, urinary tract infection, and sepsis among children receiving thrombolysis, compared with 23 (0.8%) cases of intracranial hemorrhage, <10 (0.2%) myocardial infar-
We report the first study to estimate the national rate of thrombolytic therapy for ischemic stroke in children in the United States. Based on data from the NIS, from 2000 to 2003, <2% of children with ischemic stroke received thrombolytic therapy. Children who received thrombolytic therapy were more likely to be male, white, >11 years, and had higher rates of dependency and mortality than children who did not receive thrombolytic therapy.

The data in our study must be considered in the context of certain limitations of the analysis. We used data from the NIS, a large size data set with standardized methodology representative of the United States, eliminating the bias observed in local and community based studies. However, the weighted estimates have more variability than expected from the magnitude of the numbers presented. The relatively infrequent occurrence of pediatric patients receiving thrombolysis for stroke led to final estimates based on small numbers of inpatient records with possible under-representation of certain demographic groups such as females. This low female sample size does not affect our conclusion because the occurrence of stroke in pediatric patients is not correlated with their gender. Adult men are associated with a higher incidence of strokes only because they typically engage in more high-risk behaviors (ie, drinking, smoking). These behaviors are not part of the lifestyle of the normal child, making gender an irrelevant factor in statistical evaluation. Therefore, we can only conclude from the total number of pediatric stroke patients those who receive thrombolysis or not receive thrombolysis.

The overall rate of 1.6% of thrombolysis among all pediatric ischemic stroke patients is much lower than the highly variable rates of 3% to 20% reported for adult stroke patients, though it is higher than generally accepted rates among children. Alternate indications for thrombolysis such as venous thromboembolism may have adulterated our results, though we excluded patients with a primary diagnosis of deep venous thrombosis and pulmonary embolism from the analysis.

Risk factors for pediatric stroke, as identified by associated medical conditions, were not reported for most of the children in this study, and only pneumonia and deep venous thrombosis were reported as complicating illnesses for children with thrombolysis. The most frequently reported risk factors for ischemic stroke in children are cardiac disorders, hematological disorders, metabolic disorders, arteriopathies, and infection. Risk factors identified in previous reports of children receiving thrombolytic therapy include stenocclusive disease, arterial dissection, or other thrombotic conditions, though in most series, the extent of the evaluation was limited, and no risk factors are identified in over 20% of cases. It is unclear why the rates of stroke risk
factors were so low among the patients receiving thrombolysis in this study, but may be attributable to limited investigations or reporting errors, further amplified by the overall lower numbers of patients receiving thrombolytics. Additionally, reluctance of physicians to offer thrombolytics to children with underlying diseases such as sickle cell disease or moyamoya disease, for fear of the potential for hemorrhagic complications, may have also impacted these results.

We were not able to assess stroke severity at baseline, time to treatment, dosage, and long-term outcome with the variables collected in the NIS. Thus, though a greater percentage of patients receiving thrombolysis required mechanical ventilation during their hospitalization compared with other children with stroke, it is not clear whether the former group required assisted ventilation before treatment. There have been several small reports and series of children receiving thrombolytic therapy.5-11 Most involved cases of intra-arterial delivery of thrombolytic (urokinase, tissue plasminogen activator) with varying stroke etiologies, treatment windows, dosages and outcome measures, though largely the immediate results were favorable. Mode of delivery could also not be ascertained, though it is possible that the patients who underwent cerebral angiography on the incident stroke day did so for the purposes of intra-arterial delivery of thrombolytics. Further prospective studies would be needed to identify treatment patterns and benefits and risks associated with dose ranges and modes of delivery.

Though it is widely believed that children have a greater capacity than adults for recovery after neurological insults,19,20 the majority of children with ischemic stroke will develop some motor or cognitive abnormality. A study of pediatric stroke from the Toronto Hospital for Sick Children revealed that after a mean of 2.1 years of follow-up only 31% were neurologically normal.19 Fatality rates for pediatric stroke have ranged from 0% to 21%.21 Though in the NIS dataset there were no reports of intracranial hemorrhage among the group receiving thrombolysis, children receiving thrombolysis had higher mortality rates, and discharge to a skilled nursing facility, with lower rates of routine or short-term rehabilitation center discharges. It is unclear whether these results were attributable to selection bias or adverse effects of thrombolytic therapy in children with stroke. A larger prospective clinical trial would more suitably address the issue of efficacy and safety of thrombolysis among children with ischemic stroke.

Despite lower rates of pediatric stroke compared with adults the financial burden of pediatric stroke is substantial, attributable to extended hospital stays, loss of decades of productive years of life and extended periods of supportive care in skilled nursing facilities.22-24 We found that the length of hospitalization and median costs for children with stroke were significantly higher among children receiving thrombolysis ($81,800 versus $38,700).

Our study represents 20% of all community hospital admissions in the United States, and thus far establishes the largest series of pediatric stroke thrombolysis, and the first study to report mean costs for stroke hospitalizations in children. However, patient selection based on ICD-9 coding may have biased the total number of stroke patients and those receiving thrombolysis in our study. The sensitivity and specificity of ICD-9 coding for arterial ischemic stroke in children has not been determined. Adult stroke studies using ICD-9 coding have varied in accuracy.25-26 The use of all discharge diagnostic codes classifying adult ischemic stroke has a sensitivity of 86%, specificity of 95%, and positive predictive value of 90%.27 and the sensitivity for the 99.10 code for thrombolysis has been reported as low as 55%, though the specificity may be as high as 98%.28 Furthermore, during the time period of this study, no specific code for intra-arterial modes of thrombolysis existed, and is therefore undifferentiated in the NIS database.

Conclusions

Arterial ischemic stroke is a well-recognized cause of morbidity and mortality in children. The acute treatment and prevention of pediatric stroke is based on limited studies in children. Although the use of thrombolytic therapy is being used in children with stroke, the safety and efficacy has not been established. Further studies are needed to evaluate the proper dosage, safety, and efficacy of thrombolytic agents in children with stroke.

Disclosures

None.

References


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