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Original Article

Use and In-Hospital Outcomes of Recombinant Tissue Plasminogen Activator in Pediatric Arterial Ischemic Stroke Patients

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BACKGROUND: Outcomes in pediatric stroke are poorly understood. We sought to determine trends in the use of recombinant tissue plasminogen activator (rt-PA), treatment outcomes, and predictors of mortality for pediatric patients with acute ischemic stroke by using the Nationwide Inpatient Sample. **METHODS:** Using Nationwide Inpatient Sample data from 2001 to 2010, we identified pediatric patients (age 30 days to 18 years) with the primary diagnosis of arterial ischemic stroke. We studied trends of use of intravenous rt-PA and outcomes after thrombolysis. We also analyzed the associations of demographic factors, comorbidities, and complications of arterial ischemic stroke with in-hospital mortality. **RESULTS:** This study included 7044 patients. In-hospital mortality was 4.7%. The comorbidities associated with the greatest rates of in-hospital mortality were mitochondrial disorders (19.5%, $P < 0.0001$) and hypercoagulable states (11.4%, $P < 0.0001$). The main complications associated with increased mortality were intracerebral hemorrhage (19.9%, $P < 0.0001$), sepsis (13.2%, $P < 0.0001$), and pneumonia (9.3%, $P = 0.0007$). The rate of rt-PA use was 1.4% (99 patients). rt-PA use increased from 0.9% of patients in 2001-2005 to 2.0% in 2006-2010 ($P < 0.0001$). Among patients who received rt-PA, the rate of intracerebral hemorrhage was low and without fatalities; however, there was an increased discharge-to-long-term-facilities rate in the rt-PA group (50.8% versus 12.1%, $P < 0.0001$). **CONCLUSION:** Arterial ischemic stroke in the pediatric population is associated with a greater rate of mortality when related to mitochondrial diseases or hypercoagulability. rt-PA use is increasing in pediatric patients with arterial ischemic stroke. Pediatric patients receiving rt-PA have a low risk of fatal hemorrhage. Although patients receiving rt-PA have a morbidity rate, these individuals may have a worse stroke severity.

Keywords: stroke, epidemiology, thrombolysis, pediatric

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Introduction

The reported prevalence of pediatric arterial ischemic stroke is increasing with a reported incidence of 1-3 per 100,000 patients.[1,2] Arterial ischemic stroke in this age group is associated with different comorbid conditions and mechanisms of ischemia compared with adults. The frequency and prognostic impact of secondary neurological and systemic complications also differ. Treatment standards are less well defined than in adults. The use of intravenous recombinant tissue plasminogen activator (IV rt-PA) in the pediatric population is not recommended by multiple societies because of a paucity of data.[3-6] Yet, intravenous thrombolysis is used in practice in selected cases.[7] There is very little literature addressing mortality predictors, use of rt-PA, and overall morbidity among children. The purpose of this study is to evaluate predictors of mortality and trends of rt-PA use during a 10-year period in hospitalized pediatric patients with arterial ischemic stroke.

Materials and Methods

Patient population

Data from the Nationwide Inpatient Sample (NIS) hospital discharge database concerning the years 2001-2010 were obtained from the Healthcare Cost and Utilization Project of the Agency for Healthcare

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Research and Quality. This database represents 20% of all inpatient discharges from nonfederal hospitals in the United States. Because this database is publically available, this study was considered exempt from institutional review board approval by our Institutional Review Board. Patients included in this study were younger than 18 years and had a primary diagnosis of arterial ischemic stroke and were identified using *International Classification of Diseases*, 9th Revision (ICD-9) codes of 433, 434, 436, 437.0, 437.1, 437.4, 437.5, 437.7, 437.8, and 437.9. No codes for cerebral venous infarction were included.

Demographic characteristics

Demographic information analyzed included age, sex, and race (white versus nonwhite). Each group was stratified by years (2001-2005 and 2006-2010) and rt-PA use to assess for temporal trends. Age was categorized infant/toddler (30 days-4 years), children (5-9 years), preteen (10-14 years), and teenager (15-17 years). Neonates (<30 days) were excluded because of the difficulty in excluding in utero events as a cause of stroke among neonates.

Medical comorbidities and complications

Comorbidities and complications included in this study were moyamoya (ICD-9:437.5), sickle cell disease (ICD-9:282.6), patent foramen ovale (PFO) (ICD-9:7455/7456), congenital heart disease (CCS:213), dissections (ICD-9:44100-44329), hypercoagulable state/thrombophilia (ICD-9:286.9) intracerebral hemorrhage (ICH; ICD-9:431), pneumonia (CCS:122), urinary tract infection (CCS:159), sepsis (CCS:2), pulmonary embolism (ICD-9:41511-41519), deep venous thrombosis (CCS:118), mitochondrial disease (ICD:277.87), connective tissue disease (CCS: 210), malignancy (CCS: 11-45), meningitis (CCS: 76) trauma (CCS 2601-2615), and cerebral vasculitis (ICD-9:4374). The Charlson Comorbidity Index was calculated for each patient. The Index is a weighted index that takes into account various comorbid diseases that might alter the risk of mortality in longitudinal studies and has been found to be associated with both short- and long-term mortality.[8]

Interventions and therapies

Using ICD-9 procedure codes, we categorized patients based on the treatment they received. Data regarding rt-PA therapy administration were extrapolated with the ICD-9 procedure code 9910. Patients who underwent cerebral angiography, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) were identified with the ICD-9 procedure codes of CCS:118, CCS:216 and ICD-9 3961/3965/3966, respectively. Patients undergoing cardiac surgery were identified using CCS codes 43-44 and 48-50, and patients undergoing cardiac catheterization were identified using CCS code 47.

Outcomes

The primary end points of this study were rt-PA use and in-hospital mortality rates. Secondary outcomes included rate of ICH and discharge disposition (discharge to short-term or long-term facility). Rates of ICH, discharge disposition, and mortality were compared for patients who received rt-PA versus those who did not. When determining rt-PA use rates, we performed a separate subgroup analysis excluding patients who would not typically be considered for rt-PA administration. Thus, patients with sickle cell disease, cancer, trauma, ECMO, moyamoya, mitochondrial disease, and postsurgical patients were excluded from this subgroup analysis.

Statistical analysis

χ^2 tests were used to compare categorical variables, and the Student *t* test was used to compare continuous variables assuming statistical significance at $P < 0.05$. *P*-values for outcomes were obtained using the "no rt-PA" as a reference group. Discharge weights were applied. A multivariate analysis was fit to determine comorbidities and demographic characteristics associated with mortality. All comorbidities and demographic factors were forced into this model. All statistical analysis was performed by using the SAS-based statistical package JMP (www.jmp.com; SAS, Cary, NC).

Results

Patient population

A total of 7044 hospitalized patients younger than 18 years of age were assigned a primary diagnosis of arterial ischemic stroke. Mean age was 8.6 ± 13.2 years. Patients 30 days-4 years old made up the largest age group (2280 patients, 32.2%) and patients 5-9 years old comprised the smallest age group (1479 patients, 20.9%). 99 patients (1.4%) received thrombolysis. In-hospital mortality occurred in 329 patients (4.7%). Congenital heart disease, hypercoagulable states, and sickle cell disease were the most common comorbid conditions associated with ischemic stroke. These data are summarized in Table 1.

rt-PA use rates and outcomes

The average age among rt-PA patients was 12.4 ± 9.4 years. rt-PA use was greatest in patients 10-14 years (N = 50, 3.2%) and 15-17 years old (N = 31, 1.8%). From 2001-2005 to 2006-2010, rt-PA use rates increased from 0.9% to 2.0% ($P = 0.0003$). There was an increased rate of discharged-to-long-term facilities during these two time periods from 11.1% to 15.5% ($P = 0.002$) and a decreased mortality from 5.6% to 3.6% ($P < 0.0001$). Data are summarized in Table 2.

As a whole, rt-PA patients were older than non-rt-PA patients (12.4 ± 9.4 versus 8.5 ± 13.2, $P < .0001$). The most common comorbidities in the rt-PA patient group were hypercoagulable state (24.2%) and congenital heart disease

TABLE 1.
Demographics and Outcomes of Pediatric Ischemic Stroke Patients

Variable	
Total N	7044
Age distribution	
Age, mean (SD)	8.6 (13.2)
30 days-4 years, n (%)	2280 (32.2)
5-9 years, n (%)	1479 (20.9)
10-14 years, n (%)	1570 (22.3)
15-17 years, n (%)	1716 (24.4)
Sex	
Male, n (%)	3970 (56.6)
Race	
White, n (%)	2607 (48.2)
CCI, mean (SD)	1.2 (1.4)
Outcomes, n (%)	
rt-PA use	99 (1.4)
ICH	110 (1.6)
Discharge to home	4821 (68.4)
Discharge to short-term facility	524 (7.4)
Discharge to long-term facility	921 (13.1)
Mortality	329 (4.7)
LOS, mean (SD)	8.6 (27.0)

Abbreviations:
CCI = Charlson Comorbidity Index
ICH = Intracerebral hemorrhage
LOS = Length of stay
rt-PA = Recombinant tissue plasminogen activator
SD = Standard deviation