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Endovascular therapy in pediatric stroke: utilization, patient characteristics, and outcomes

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Abstract

Background and Purpose—Despite strong evidence for endovascular therapy in adults with acute arterial ischemic stroke, limited data exists in children. We aimed to describe endovascular therapy utilization and explore outcomes in a national sample of pediatric arterial ischemic stroke.

Methods—We queried the 2012 Kids' Inpatient Database for children aged >28 days to 20 years with ICD-9-CM codes for arterial ischemic stroke and evaluated groups based on procedure code for endovascular therapy. Poor outcome was defined as need for tracheostomy or gastrostomy, discharge to rehabilitation facility, or death. Logistic regression evaluated the association between endovascular therapy and poor outcome, adjusted for age, disease severity (hemiplegia, critical care interventions, neurosurgical interventions), and comorbidities.

Results—We identified 3184 pediatric discharges with a diagnosis code for arterial ischemic stroke. Thirty-eight (1%) had an endovascular therapy procedure code. Endovascular therapy patients were older (10.2 versus 4.5 years, $p<.001$), and more likely to have hemiplegia/paresis (RR 3.8, 95% CI 2.0–7.4), aphasia (RR 5.3, 95% CI 2.8–10.1), and facial droop (RR 4.0, 95% CI 1.9–8.7). Endovascular therapy was not associated with critical care and neurosurgical interventions or intracranial hemorrhage. Length of hospitalization, mortality, and discharge disposition were similar between groups. In a multivariable model, endovascular therapy was not associated with poor outcome (aOR 1.7, 95% CI 0.7–4.1).

Conclusions—In a national sample of children with a diagnosis of arterial ischemic stroke, endovascular therapy was infrequently utilized. Patients with a procedure code for endovascular therapy had significant stroke-related deficits, but outcomes were similar to children who did not receive endovascular therapy. Our data in conjunction with evidence of benefit in adults support consideration of endovascular therapy for select children with acute stroke.

Keywords

pediatric stroke; endovascular treatment; ischemic stroke; thrombectomy; outcomes research

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Conflicts of interest: none

Arterial ischemic stroke (AIS) occurs in 1–8/100,000 children per year,^{1–3} leaving 60% with permanent neurologic deficits.^{4, 5} The diagnosis of AIS is often delayed in children who are more likely to have a stroke mimic.⁶ This delay makes it more difficult to offer acute therapies to children and to study in controlled trials.

In adults, acute therapies including intravenous tissue plasminogen activator (tPA) and endovascular therapy are established as beneficial. Endovascular therapies are catheter-based interventions to recanalize the vessel, including intra-arterial thrombolysis and mechanical techniques such as stent retrieval.⁷ The 2015 AHA guidelines which recommend endovascular therapy for adults presenting within 6 hours with large vessel occlusion, also state that use of endovascular therapy with stent retrievers may be reasonable in children < 18 years.⁸

No clinical trials have evaluated outcomes of pediatric endovascular therapy, with evidence coming from case reports and single center series.^{9–14} We aimed to report the utilization of endovascular therapy in pediatric AIS, identify characteristics associated with receipt of endovascular therapy, and explore associated outcomes among a nationally representative sample of children with AIS in the United States (US).

Methods

We performed a retrospective cohort analysis of administrative data within the 2012 Kids Inpatient Database (KID) from the Agency of Healthcare Research and Quality¹⁵ to evaluate the utilization of endovascular therapy in pediatric AIS and to explore characteristics and outcomes associated with endovascular therapy. The 2012 KID contains pediatric discharges from 44 states and 4,179 hospitals for children ages 20 years and younger in the US. The large sample size and stratified probability sampling design allows for national estimates using weighting procedures. The KID includes demographic information, payer, hospital characteristics, ICD-9-CM diagnosis codes, ICD-9-CM procedure codes, clinical classification software (CCS) codes that group ICD-9-CM diagnosis and procedure codes, length of stay, hospital charges, admission and discharge status, and in-hospital death. The data are anonymous. Use of the KID is considered non-human subjects research and is exempt from Oregon Health and Science University's institutional review board evaluation.

We identified AIS patients aged >28 days to 20 years with ICD-9-CM diagnosis codes for pre-cerebral (433; includes basilar, vertebral, carotid) and cerebral arterial occlusions or narrowing (434). We limited our AIS cohort to codes 433 and 434, which have the best reported true positive rates for diagnosis codes among inpatients with arterial ischemic strokes.^{16–18} The endovascular therapy group was identified by an ICD-9-CM procedure code for endovascular thrombectomy or embolectomy (39.74). Demographic and clinical characteristics were evaluated by groups of endovascular therapy versus other therapy (patients without an endovascular therapy procedure code). ICD-9-CM diagnosis, ICD-9-CM procedure, and CCS codes were used to define other variables and compare by groups (please see online supplement). We also created comorbidity categories for analysis from variable coding outlined in the online supplement. Critical care interventions were defined as mechanical ventilation, non-invasive ventilation, intracranial pressure monitor, arterial

catheterization, or central venous catheterization. Neurosurgical interventions were defined as decompressive craniectomy, intracranial hematoma drainage, ventriculoperitoneal shunt, or externalized ventricular drain. We created a composite variable to define poor outcome as need for tracheostomy or gastrostomy during hospitalization, in-hospital mortality, or discharge to a nursing or rehabilitation facility.

Analyses were conducted in SPSS for Windows (Version 23, IBM Corporation) with the complex samples add-on. National weighted estimates and their standard errors were calculated. The finite population correction was used to adjust standard errors because results were not generalized beyond 2012 and because the KID contains a large percentage of children treated in US hospitals. All weighted estimates were rounded to the nearest whole number. Per the KID data use agreement, estimates with totals > 0 and 10 are not reported in results. Calculation of population incidence was performed using US census data.⁷ Categorical variable estimates were rounded to whole numbers and percentages. Continuous variable estimates were expressed as means with standard error. Bivariate analyses used Chi-Square tests with Fisher Exact correction for categorical variables and t-tests for continuous variables. Bivariate results were reported with p-values and Relative Risk (RR) with 95% Confidence Interval (CI) for categorical variables. A p-value of <.05 defined statistical significance. A logistic regression model for “poor outcome” was created to evaluate the association between endovascular therapy and poor outcome adjusted for patient age, disease severity (hemiplegia, critical care interventions, neurosurgical interventions), and comorbidity categories. Multivariable model results were reported as adjusted Odds Ratio (aOR) and 95% CI.

Results

AIS codes were identified in 3184 pediatric discharges, corresponding to an incidence of 3.7 cases/100,000 US children in 2012. Endovascular therapy procedure codes were identified in 38 (1%) patients. Table 1 presents demographic and admission characteristics by endovascular therapy group. Endovascular therapy patients ranged from 2–20 years, with 78% 11 years, and endovascular therapy patients were significantly older (10.2 versus 4.5 years, $p < .001$). Overall, 47% of AIS patients were female and endovascular therapy did not vary with sex. Government sponsored insurance (Medicaid) was less common in the endovascular therapy group (RR 0.2, 95% CI 0.1–0.6). However, endovascular therapy was more common in public versus privately owned hospitals (RR 3.1, 95% CI 1.6–6.1). Children with AIS were infrequently treated at freestanding children’s hospitals, and receipt of endovascular therapy did not differ by type of hospital ($p=.17$).

Clinical characteristics by endovascular therapy group are presented in Table 2. Overall, 13% of children with AIS had carotid vessel occlusion codes. Codes for basilar or vertebral occlusions were seen in 4% of all AIS patients with a non-significant trend toward higher rates in the endovascular therapy group (RR 3.0, 95% CI 1.0–8.3). Overall, 71% had at least one comorbid condition identified as an AIS risk factor. Cardiac comorbidities were most common in both groups (42% endovascular therapy versus 28% other, $p=.07$). Congenital heart disease accounted for the majority of the difference between the groups in the cardiac category. Other comorbid categories were similar including arteriopathy, systemic disorders,

head and neck disorders, and hypercoagulable states. The frequency of sickle cell disease was not different between groups, though the numbers in the endovascular therapy group were very small. Endovascular therapy patients were more likely to have significant stroke-related symptoms during their hospitalization, including hemiplegia or paresis (RR 3.8, 95% CI 2.0–7.4), aphasia (RR 5.3, 95% CI 2.8–10.1), and facial droop (RR 4.0, 95% CI 1.9–8.7). Seizure was significantly less common in the endovascular therapy group (RR 0.2, 95% CI 0.1–0.7); seizure incidence decreased significantly with increasing age ($p<.001$).

Table 3 presents hospital procedures and therapies by endovascular therapy group. Critical care interventions were common, occurring in 43% of children with AIS, and did not differ by endovascular therapy group. No patients in the endovascular therapy group received blood product transfusions, while 17% in the standard therapy group received packed red cell transfusions during admission ($p=.002$). Of the 520 patients who received transfusions, 17% had sickle cell disease. TPA administration was uncommon overall (2%), but was significantly more common in the endovascular therapy group (RR 33.6, 95% CI 18.4–61.3). TPA administration increased with increasing patient age ($p=.01$). Neurosurgical interventions were uncommon, occurring in 3–4% of patients in both groups ($p>.99$).

Outcomes were similar in both groups (Table 3). Intracranial hemorrhage occurred in 8% of all children with AIS, and did not differ by endovascular therapy group ($p=.12$). Intracranial hemorrhage varied with tPA (22% among patients with endovascular therapy and tPA, 10% among tPA only patients, 7% among endovascular therapy only patients, 8% among patients with neither tPA nor endovascular therapy codes). However, patient numbers were low and intracranial hemorrhage was not significantly associated with endovascular therapy and tPA combination compared to other groups ($p=.06$) or with tPA overall ($p=.16$). In-hospital mortality was 10% and did not differ by endovascular therapy group. Lengths of stay and hospital charges were also similar. Poor outcome, defined as need for tracheostomy, gastrostomy, discharge to rehabilitation facility, or death, did not differ by group (45% endovascular therapy versus 30% other, $p=.07$). In a multivariable model of poor outcome adjusted for patient age, disease severity (hemiplegia, critical care intervention, neurosurgical intervention), and comorbidity categories, endovascular therapy was not associated with poor outcome (aOR 1.7, 95% CI 0.7–4.1).

Discussion

Among a national sample of >3,000 pediatric discharges with AIS codes, 1% had procedures codes for endovascular therapy, encompassing the largest cohort of pediatric endovascular therapy reported to date. Children in the endovascular therapy group were older, often had cardiac comorbidities, and were more likely to have substantial neurologic deficits. Adding to the limited safety data for pediatric endovascular therapy, rates of significant complications, such as intracranial hemorrhage and need for critical care or neurosurgical procedures, did not differ with endovascular therapy. Our data showed no difference in hospital mortality or poor outcome with endovascular therapy.

We found a pediatric AIS incidence of 3.7/100,000 US children in 2012. Studies of ischemic stroke in children report incidences ranging from 0.6–7.9/100,000 children per year.

2, 3, 16, 19–26 Our incidence is consistent with recent studies using similar populations and methods.^{22, 24} We found endovascular therapy codes in 1% of our AIS cohort. This is consistent with early utilization rates in adults with ischemic stroke (0.6% in 2009)²⁷ and with estimates from single center reports performing about 0.5 endovascular therapy cases per year in children.^{12, 13} In 2012, endovascular therapy was not a universally accepted therapy in adults, potentially limiting pediatric utilization.²⁸ Diagnostic delay reported in pediatric stroke may limit utilization of acute therapies like endovascular therapy.^{6, 29} Institutional and technical factors may preclude endovascular therapy in younger patients, including limited access to facilities or providers capable of performing endovascular therapy in children, and lack of pediatric-specific devices.

TPA was given to 2% of patients overall, comparable to other reports.³⁰ TPA was more common in the endovascular therapy group, which is not surprising given the overlap in eligibility for these therapies. There may also be a center or provider bias toward more intervention. Additionally, this dataset does not distinguish intravenous tPA from intra-arterial tPA, so the overlap may be explained by patients who received intra-arterial tPA in the context of their endovascular procedure.

Children with substantial deficits like hemiparesis were significantly more common in the endovascular therapy group, which may reflect large vessel occlusion or earlier recognition of stroke. Medicaid insurance was less common in the endovascular therapy group. Children with Medicaid have been shown to have worse outcomes in a number of disease states.^{31–33} Among adult stroke patients, African-Americans, the uninsured, and Medicare patients have been shown to be less likely to receive endovascular therapy.³⁴ The impact of insurance status, socioeconomic status, and race on pediatric stroke interventions, access to care, and outcomes is an area that warrants further study.

Seizure was less common in the endovascular therapy group, which may be explained by the higher rates of seizures in younger children in this cohort, consistent with other reports in pediatric stroke.³⁵ Seizure presentation has not been associated with delay in pediatric stroke diagnosis.^{29, 36} Nonetheless, it is possible that children presenting with seizure and motor deficits are initially presumed to have a Todd's paralysis, precluding a diagnosis within a window for acute intervention. Alternatively, patients with seizure at presentation may have been miscoded as having a stroke. Notably, 42% of patients in the endovascular therapy group had a cardiac comorbidity, portending high risk for embolism and large vessel occlusion. This is consistent with a review of case reports, in which 34.5% of children receiving endovascular therapy had cardiac pathology.³⁷ Stroke programs planning for pediatric endovascular therapy need to consider the factors unique to cardiac patients such as vascular anatomic differences and higher likelihood of being hospitalized at the time of stroke onset.

Endovascular therapy is established as beneficial in adult stroke, though data is limited in children. In adults, five trials between 2010 and 2015 demonstrated efficacy of endovascular therapy using stent retrievers in anterior circulation stroke.^{38–42} These trials showed significant improvements in the Modified Rankin Scale (MRS). Efficacy of endovascular therapy in children is not known, though a recent review of the 29 published cases of

mechanical thrombectomy using modern devices in children was encouraging, with no deaths and 86.7% having a good outcome defined as MRS ≤ 2 .³⁷ A historical comparison group of children with large vessel occlusion not receiving endovascular therapy has not been reported, making it difficult to draw definitive conclusions about the efficacy of endovascular therapy in children from case reports.

Outcomes in our study were not associated with endovascular therapy. Though disability measures are not available through KID, our data on mortality and complications are likely to be more representative of the population of children undergoing endovascular therapy versus case reports and series when considering publication bias. Our study found 45% of the endovascular therapy group had a poor outcome and mortality was 10%, though this did not differ from the group without endovascular therapy codes. In a subgroup analysis of patients with codes for pre-cerebral occlusion and hemiparesis, we found no differences in outcomes with endovascular therapy procedure code, though numbers were small. It was encouraging that even though the endovascular therapy patients had more frequent severe deficits such as hemiparesis during hospitalization, they did not differ in outcome measurements from other AIS patients in our cohort.

Patients in the endovascular therapy group without procedure codes for tPA were at no higher risk of hemorrhage than other AIS patients, though patients with the combination of codes for endovascular therapy and tPA trended toward higher rates of hemorrhage. In the few reported cases of combined intravenous tPA and endovascular therapy in children, hemorrhage was not reported.^{11, 43, 44} A review of 34 patients treated with endovascular therapy reported hemorrhage in 23.5%, all of whom were treated with intra-arterial tPA.¹⁰ Data from adult stroke trials supports about a three-fold higher hemorrhage rate with intra-arterial thrombolysis, with rates around 10%.⁴⁵ We suspect the trend toward higher rates of hemorrhage seen in the group with procedure codes for both tPA and endovascular therapy may be due to the use of intra-arterial tPA, though rates were still higher than those reported in adults, warranting further evaluation of the use of tPA and endovascular therapy in combination among pediatric patients.

This study is based on administrative data which allows for evaluation of a large sample of hospitalized children, which is useful for exploring outcomes after an infrequently performed procedure, though the small number of patients with endovascular therapy codes may have limited some analyses. However, the use of administrative data comes with the limitation that AIS and endovascular therapy patients are included based on diagnostic and procedure codes, and could not be confirmed with chart review. The sensitivity and specificity of ICD-9 codes for stroke vary based on population studied, with a positive predictive value of 77–84% in pediatric studies.^{16, 17} The limited sensitivity and specificity of the ICD-9-CM stroke codes means our overall cohort of AIS patients likely includes some patients without AIS and does not capture some patients with AIS. The large sample size and high sampling frequency of pediatric discharges within KID yield a nationally representative sample that helps mitigate this limitation and KID studies have produced similar incidences to other research methods in a variety of pediatric diseases.^{46–48} Additionally, KID does not include information on devices or techniques used, which have evolved since 2012. Details of clinical symptoms at presentation, National Institutes of

Health Stroke Scale Score, time to therapy, repeated admissions, laboratory data, residual discharge deficits, and outcome past discharge are not available in this dataset.

Summary

Among a national cohort of children with a diagnosis code for AIS, 1% had a procedure code for endovascular therapy. Patients in the endovascular therapy group were older and had substantial neurologic deficits. Outcomes and complications including death, neurosurgical procedure, hemorrhage, discharge status, and length of hospitalization were not different among patients in the endovascular therapy group, adding to the limited safety data for pediatric endovascular therapy. While endovascular therapy merits consideration in children with acute stroke, further research is needed to understand if this therapy improves outcomes in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.**Demographic and Admission Characteristics by Receipt of Endovascular Therapy**

	Endovascular Therapy N= 38 (%)	Other Therapy N= 3146 (%)	p-value
Average Age (SEM)	10.2 (.23)	4.5 (.05)	<.001
Female Sex	21 (55%)	1479 (47%)	.33
Race/Ethnicity			.41
White	14 (36%)	1434 (46%)	
Hispanic	10	517 (16%)	
Black	10	579 (18%)	
Other or not reported	10	616 (20%)	
Payer			.004
Government	10	1423 (45%)	
Private	25 (67%)	1355 (43%)	
Other or self-pay	10	357 (11%)	
Missing	0	10	
Admission Source			.86
Emergency Room	20 (52%)	1483 (47%)	
Transfer from acute care facility	10	813 (26%)	
Transfer from other health facility	10	95 (3%)	
Hospital Region			.19
Northeast	10	518 (17%)	
Midwest	10	720 (23%)	
South	10	1153 (37%)	
West	14 (36%)	754 (24%)	
Children's Hospital	10	1091 (35%)	.17
Hospital Classification			.88
Rural	10	57 (2%)	
Urban non-teaching	10	298 (10%)	
Urban teaching	34 (89%)	2791 (89%)	
Hospital Control			.001
Government	13 (35%)	441 (14%)	
Private, non-profit	23 (62%)	2501 (80%)	
For profit	10	203 (7%)	

Per the Kids' Inpatient Database data use agreement, weighted estimates with values 10 cases are not reported. All reported values are weighted estimates rounded to the nearest whole number or percentage and may not sum to totals.

Abbreviations: SEM-standard error of mean

Table 2.

Clinical Characteristics of Patients by Receipt of Endovascular Therapy

	Endovascular Therapy N=38 (%)	Other Therapy N= 3146 (%)	p-value
Precerebral Arterial Occlusion	11 (29%)	529 (17%)	.08
Basilar or Vertebral occlusion	10	117 (4%)	.05
Any comorbidity category identified	31 (82%)	2224 (71%)	.16
Comorbidity Category			
Cardiac category	16 (42%)	886 (28%)	.07
Arteriopathy category	10	527 (17%)	.82
Systemic category	10	670 (21%)	.69
Head and neck category	10	760 (24%)	.06
Hypercoagulable category	10	181 (6%)	.28
Hemiplegia or paresis	24 (64%)	955 (30%)	<.001
Aphasia	14 (38%)	302 (10%)	<.001
Facial droop	10	190 (6%)	.002
Blindness or visual deficit	10	231 (7%)	.76
Cerebellar symptoms	10	251 (8%)	.36
Cerebral edema	10	473 (15%)	.07
Seizure	10	974 (31%)	.004
Hydrocephalus	10	223 (7%)	.75
Encephalopathy	10	291 (9%)	.78
Hypertension	10	439 (14%)	.35

Per the Kids' Inpatient Database data use agreement, weighted estimates with values 10 cases are not reported. All reported values are weighted estimates rounded to the nearest whole number or percentage and may not sum to totals.

Table 3.

Hospital procedures, adjunct therapies, and patient outcomes

	Endovascular Therapy N=38 (%)	Other Therapy N= 3146 (%)	p-value
Any critical care intervention	14 (37%)	1367 (43%)	.51
Red blood cell transfusion	0	520 (17%)	.002
Platelet transfusion	0	144 (5%)	.42
Plasma transfusion	0	160 (5%)	.26
TPA administration	19 (51%)	73 (2%)	<.001
Any neurosurgical intervention	10	119 (4%)	>.99
Death in hospital	10	311 (10%)	>.99
Routine discharge	17 (45%)	1801 (57%)	.14
Poor outcome	17 (45%)	948 (30%)	.07
Average Length of Stay in Days (SEM)	11.2 (1.3)	16.1 (.6)	.40
Average Hospital Charges in Thousand Dollars (SEM)	288 (67)	220 (11)	.50

Per the Kids' Inpatient Database data use agreement, weighted estimates with values 10 cases are not reported. All reported values are weighted estimates rounded to the nearest whole number or percentage and may not sum to totals.

Abbreviations: SEM-standard error of mean