pediatric stroke

Original Research Contribution

Anti-seizure Medication Practice Variation by Age of Pediatric Arterial Ischemic Stroke

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Abstract

Providers commonly initiate anti-seizure medications (ASMs) for seizure management after pediatric arterial ischemic stroke. However, optimal management and duration of treatment to minimize adverse effects and prevent recurrent seizures is unknown. We sought to examine practice variation and factors that influence ASM management one year after pediatric stroke.

Seizures in Pediatric Stroke (SIPS) is a prospective observational study conducted across 21 international sites that collected data about seizures and ASMs for 12 months after neonatal (birth – 28 days) or childhood (29 days-18 years) arterial ischemic stroke. Multivariable analysis determined factors associated with one-year ASM use in those with acute seizures.

Of 56 study subjects (26 neonates) who had a seizure within seven days post-stroke, 50 (89%) were discharged on ASMs. Eleven (20%) had seizures post-hospital discharge, and 21 (38%) remained on ASMs at 12-months. No child reported seizures after stopping ASMs. Neonates were less likely to be treated with ASMs at 12-months than older children (Odds Ratio 31.1, 95% confidence interval 2.5- 384.7, p=0.002), even after adjusting for having many acute seizures and seizures post-hospital discharge.

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Providers discontinue ASMs earlier after neonatal stroke than childhood stroke, but it is unclear whether prolonged therapy in older children is warranted.

Introduction

Acute symptomatic seizures are common in neonatal and childhood arterial ischemic stroke (AIS), occur more frequently in younger children compared to older children or adults, and are associated with a higher risk of post-stroke epilepsy.[1-4] Pediatric stroke guidelines recommend supportive care including control of acute symptomatic seizures when they occur[5, 6], but do not provide guidance for starting a maintenance ASM or treatment duration. Although supporting evidence is low, the World Health Organization recommends consideration of discontinuing ASMs when a neonate is seizure free for more than 72 hours.[7]

Stroke-associated seizure management in adults is also controversial, with open questions about whether a seizure requires treatment and for what duration.[8] European guidelines for management of post-stroke seizures in adults recommend against using ASMs in most instances because of low seizure incidence in adults, and withdrawing the ASM after the acute phase if one is started.[9] However, all recommendations were considered weak in recognition of very low availability of quality evidence.

Clinicians treating a child with a post-stroke seizure must balance the potential benefit of preventing additional seizures with potential adverse effects of medications, including short and possibly long-term cognitive consequences.[10, 11] In light of these unknowns, we sought to describe the variation in management of acute seizures after AIS in the multicenter, international Seizures in Pediatric Stroke (SIPS) study. Within this cohort, we analyzed factors potentially associated with ASM treatment 1 year after stroke, including age, number or duration of acute seizures, post-hospital discharge seizures, stroke radiographic features, and provider-specific factors including site and geographic region.

Methods

Seizures in Pediatric Stroke (SIPS), a prospective observational study of acute symptomatic pediatric AIS conducted at 21 international sites, included neonates (< 28 days at stroke onset) and children (29 days through 18 years at stroke onset) enrolled 3/2011 -8/2012 as previously reported.[4] Investigators provided information about seizures and ASMs during stroke hospitalization and at 3 and 12 months post-stroke. Data collected during the stroke hospitalization included: infarct characteristics, number of acute seizures (occurring <7 days after stroke including seizures at presentation), longest duration of acute seizure, seizure occurrence

after hospital discharge and ASM use. Acute seizures reported by site investigators included clinical and/or electrographic seizures. Investigators reported an estimated number of seizures as a categorical variable: single seizure, 2- 10 seizures, or more than 10 seizures. Prolonged acute seizures were defined as lasting ≥5 minutes. If seizure duration was missing but a rescue medication was documented or patient was seizing on arrival to hospital, seizure duration was arbitrarily assigned 5 minutes. If seizure duration was missing and no rescue medication was documented, seizure duration was assigned 0.5 minutes. Site investigators reported stroke radiographic features on brain magnetic resonance imaging (MRI), including vascular territory of infarction, cortical infarcts, and any associated hemorrhage. We divided participating sites into five regions (Australia, Canada, Europe, South America, and United States) for geographic comparison.

Statistics

Statistical analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC). Only patients with acute seizures were included in analyses. We used summary statistics to describe the characteristics of the neonates, the children and overall cohort included in our analyses. We used univariate logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) of

pre-specified baseline variables potentially associated with 12-month ASM use. To determine whether the association of age at stroke (neonatal versus child) and 12 month ASM treatment was largely influenced by severity of acute seizures or post-hospital discharge seizures, we examined multivariable logistic regression models that adjusted for these variables. Because a high proportion of participants with seizures after hospital discharge were treated with an ASM at 12 months, we also performed a sensitivity analysis excluding the 11 patients with seizures after hospital discharge.

All sites obtained local institutional review board approval and written informed consent from participants and/or guardians.

Results

Of 114 neonates and children with AIS enrolled in SIPS, 57 (50%) had an acute seizure within 7 days of stroke presentation. One of the 57 participants died prior to hospital discharge. The remaining 56 neonates and children completed 12 month follow-up (Figure). Two neonates and three children with acute seizures were not treated with an ASM during their hospitalization or

after discharge; none reported a post-discharge seizure. None of the 35 children or neonates off of ASMs at 12 months reported a seizure after medication discontinuation. Demographics and baseline clinical characteristics, other than age, were similar between neonates and children (Table).

Among 26 neonatal stroke survivors with acute seizures, 24 received an ASM during their hospitalization. All 24 neonates who received ASM continued medication at discharge. At 12 months, only 4 (15% of those with neonatal stroke) were treated with an ASM. Three of the 4 neonates receiving ASM at 12 months had reported at least one seizure after discharge from the stroke hospitalization. One neonate was on two ASMs at 12 months.

Among 30 childhood stroke survivors with acute seizures, 28 (93%) received an ASM during the stroke hospitalization. At discharge, 26 continued ASMs. At 12-months, 17 (57% of those with childhood stroke) were treated with an ASM. Of these 17 children receiving ASMs at 12 months, 7 had at least one seizure after discharge from the stroke hospitalization. Two children were taking 2 ASMs, and one child was taking 3 ASMs at 12 months.

We did not identify any variables predicting ASM continuation at hospital discharge, likely due to the large proportion of children (50/56, 89%) discharged with medication. In univariate analysis, 12 month ASM treatment was associated with childhood (versus neonatal) stroke (OR 7.2 95% CI (2.0-26.1), p = 0.003), more than 10 acute symptomatic seizures (versus single acute seizure) (OR 6.6 95% CI (1.5-28.7), p=0.01), and seizure occurrence after hospital discharge (OR 30.9 95% CI (3.6-269.4) p=0.002). Twelve month ASM treatment was not associated with prolonged acute seizure, stroke vascular territory, cortical involvement of stroke, any associated cerebral hemorrhage, or geographic region of participating site. After adjusting for greater than 10 acute seizures and seizure occurrence after hospital discharge, children remained more likely than neonates (OR 31.1 95% confidence interval 2.5-384.7, p=0.007) to be treated with ASM at 12 months. In the sensitivity analysis excluding the 11 who had seizures after hospital discharge, childhood stroke survivors were more to remain on ASMs than neonatal stroke survivors in both univariable analysis (OR 16.2, 95% CI 1.8- 141.3, p=0.01) and after adjustment for greater than 10 acute seizures (OR 24.9 95% CI 2.0-292.4, p = 0.01).

Discussion

In this international pediatric stroke cohort, childhood stroke survivors were 31 times more likely to be treated with an ASM at 12-month follow-up than neonatal stroke survivors, even after adjusting for high number of seizures during hospitalization and post-hospital discharge seizures. The majority of neonates and children who experienced an acute seizure remained on an ASM at hospital discharge. After hospital discharge, we noted a discrepancy in the proportion of neonates and children who were treated with an ASM treatment at 12 months; as 96% of neonates, but only 57% of older children without post-discharge seizures were off of maintenance drugs at 12 months. We did not find geographic influence on treatment, but these analyses were limited by small numbers of participants in each of the four regions outside of the United States.

Variability of practice and timing of discontinuation of ASMs reflects the current ambiguity in recommendations for treatment of seizures associated with pediatric stroke presentation. Half of the SIPS cohort with AIS had at least one acute symptomatic seizure. The overwhelming majority was discharged on an ASM, and we did not identify any variables correlating with drug continuation at the time of hospital discharge. We did not collect information about the clinical

rationale for maintaining or withdrawing ASMs, but specific characteristics of providers or patients could have influenced management. For example, we do not know if drug-related adverse events could have resulted in earlier discontinuation. Our observation that ASM management did not correlate with infarct characteristics was limited by the lack of centralized MRI or EEG assessment; local site investigators reported clinical results. Imaging features that we did not capture in a standardized way may have influenced provider decisions to treat or not treat with an ASM, and duration of treatment. An additional limitation from variability in EEG assessment includes possible differences in seizure detection, which may explain our lack of difference in categorical number of seizures between children and neonates.

Neonatal literature has recently focused on the safety of early ASM discontinuation in all neonates. Natarajan et al. demonstrated that despite evidence, discrepancy remains between theoretical support of early discontinuation and practice.[12] While we do not have granularity to examine exact ASM duration, our study suggests providers do practice early discontinuation for neonates, even those with acute status epilepticus or multiple acute seizures. ASM management and early discontinuation for provoked (non-epilepsy) seizures in older children has not been as widely studied as in neonates.

All participants with post-hospital discharge seizures were discharged on ASM treatment. It is possible that longer duration of ASM treatment prevented seizures in a proportion of patients. However, there were no seizures reported in any neonate or child after ASM discontinuation. Fitzgerald et al. also reported low risk of seizure recurrence after ASM discontinuation in neonates with hypoxic ischemic encephalopathy.[13] Minimizing ASM exposure in all children is important, as these medications have been implicated in decreased cognitive performance, which may or may not improve after discontinuation. [14, 15]

Our study had limitations. EEG monitoring was not required for study participation. Frequency and length of continuous EEG monitoring varied across sites according to local practice. Electrographic or clinical seizures may have been underdiagnosed in some neonates and children. Finally, half of patients with AIS enrolled in SIPS had an acute symptomatic seizure and met criteria for inclusion in this analysis, but pediatric AIS overall is a relatively rare disease. The limited numbers of patients in our analyses resulted in odds ratio estimates with wide confidence intervals.

Children with acute seizures after stroke may benefit from ASMs, but the optimal duration of therapy is uncertain. Practice variability of ASM management after childhood stroke justifies future research to optimize duration of treatment and guide best practice. Better stratification of children into groups at low versus high risk for remote seizures based on clinical, electrographic, and/or radiographic data, could allow more targeted management of those who could benefit from longer duration of treatment.

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Author Contributions

KPG, CKF and GDV conceived and designed the study. KPG and CKF analyzed data and drafted the manuscript. All authors reviewed and edited the manuscript.

Conflicts of Interest

The authors do not have any conflicts of interest.

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Figure: Flow chart of participants with acute symptomatic seizures after pediatric stroke and reported anti-seizure medication (ASM) treatment.

Table. Demographics and characteristics of neonates and children with acute seizures surviving to hospital discharge.

	Total N=56	Neonate n=26	Childhood n=30	p
Male	30	13 (50%)	17(57%)	0.62
Geographic Region				0.65
Australia	8	3 (12%)	5 (17%)	
Canada	7	5 (19%)	2 (7%)	
Europe	6	2 (7%)	4 (13%)	
South America	6	3 (12%)	3 (10%)	
United States	29	13(50%)	16 (53%)	

Number of acute seizures				0.15
1	13	3 (12%)	10 (33%)	
2-10	32	18 (69%)	14 (47%)	
>10	11	5 (19%)	6 (20%)	
Duration of longest acute seizure reported in minutes (Median, IQR)		3 [1,5]	3 [1, 5]	0.82
Seizure >5 minutes	22	9 (41%)	13 (59%)	0.51
Cortical involvement	25	14 (54%)	11 (37%)	0.28
Discharged on ASM	50	24 (92%)	26 (87%)	0.67
Phenobarbital	31	23 (88%)	8(27%)	**<0.001**
Levetiracetam	19	6 (23%)	13 (43%)	0.16
Topiramate	1	0	1 (3%)	>0.99
Valproic Acid	2	0	2 (7%)	0.49
Seizures after hospital discharge	11	4 (15%)	7 (23%)	0.52
ASM at 3 month	41	18 (69%)	23 (77%)	0.56