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National Trends in Incidence Rates of Hospitalization for Stroke in Children With Sickle Cell Disease

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Abstract

Background—The success of primary stroke prevention for children with sickle cell disease (SCD) throughout the United States is unknown. Therefore, we aimed to generate national incidence rates of hospitalization for stroke in children with sickle cell disease (SCD) before and after publication of the Stroke Prevention Trial in Sickle Cell Anemia (STOP trial) in 1998.

Procedure—We performed a retrospective trend analysis of the 1993–2009 Nationwide Inpatient Sample and Kids' Inpatient Databases. Hospitalizations for SCD patients 0–18 years old with stroke were identified by ICD-9CM code. The primary outcome, the trend in annual incidence rate of hospitalization for stroke in children with SCD, was analyzed by linear regression. Incidence rates of hospitalization for stroke before and after 1998 were compared by the Wilcoxon rank-sum test.

Results—From 1993 to 2009, 2,024 hospitalizations were identified for stroke. Using the mean annual incidence rate of hospitalization for stroke from 1993 to 1998 as the baseline, the rate decreased from 1993 to 2009 (point estimate = $-0.022/100$ patient years [95% CI, -0.039 , -0.005], $P = 0.027$). The mean annual incidence rate of hospitalization stroke decreased by 45% from 0.51 per 100 patient years in 1993–1998 to 0.28 per 100 patient years in 1999–2009 ($P = 0.008$). Total hospital days and charges attributed to stroke also decreased by 45% and 24%, respectively.

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Conclusions—After publication of the STOP trial and hydroxyurea licensure in 1998, the incidence of hospitalization for stroke in children with SCD decreased across the United States, suggesting that primary stroke prevention has been effective nationwide, but opportunity for improvement remains.

Keywords

hospitalization; sickle cell disease; stroke

INTRODUCTION

Sickle cell anemia (SS) is associated with an increased risk of stroke, which occurs in approximately 10% of children with SS by 20 years of age without prevention [1,2]. Elevated transcranial Doppler ultrasonography (TCD) velocity predicts risk for stroke [3], with abnormal TCD status conferring a 10% per year risk of stroke for 3 years [4]. The Stroke Prevention Trial in sickle cell anemia (STOP trial) demonstrated a 92% decrease in the rate of stroke in children with abnormal TCD when treated with monthly erythrocyte transfusions compared to observation alone [4]. After a planned interim analysis, the STOP trial was closed early due to detection of the large effect size of the intervention, and the results were first publicized in a National Heart, Lung, and Blood Institute clinical alert in September 1997. Since that time, primary stroke prevention, the combination of TCD screening and chronic erythrocyte transfusions, has been widely regarded as the standard of care for children with SS [5].

In addition to primary stroke prevention, hydroxyurea (HU) may reduce stroke risk in pediatric SS patients. The use of HU in a pediatric SS population was first described in 1996 [6–8]. Since then, HU has been shown to reduce TCD velocities [9,10] and the risk of secondary stroke in uncontrolled studies [11–13]. The SWiTCH trial, however, failed to show that HU was non-inferior to chronic transfusions for secondary stroke prevention [14]. HU also is theorized to reduce the risk of first stroke, but this remains to be tested definitively. Since HU licensure for adults in the US in 1998, pediatric hematologists have utilized HU for SS patients to varying degrees, but with increasing frequency over time [15].

Few studies have evaluated the epidemiology of stroke in the era of primary stroke prevention and HU in the pediatric SS population. Previous estimates of stroke have been limited by a short study frame [16] or by single center design [17]. The primary goal of this study was to examine secular trends in the incidence rate of hospitalization for stroke in a national sample of children with SS. Secondary goals of this study were to examine the secular trends in total hospital days, hospital charges, and mean age of stroke. We hypothesized that the incidence rate of hospitalization for stroke would decrease after publication of the STOP trial and licensure of HU, both in 1998.

METHODS

Data Source and Study Design

This study was a retrospective trend analysis of hospitalization for stroke in children with SS using the 1993 to 2009 Nationwide Inpatient Sample (NIS) databases and the Kids' Inpatient Databases (KID) for 1997, 2000, 2003, 2006, and 2009. The NIS and KID are large administrative databases collected by multiple state and hospital agencies and administered by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The NIS approximates a 20% stratified sample of adult and pediatric hospitalizations from US community hospitals, permitting national estimates. The KID databases include only hospitalizations for children 20 years old. The KID is also weighted to permit national estimates. Because the NIS and KID are de-identified databases without unique patient identifiers, the unit of measure is a discharge, not an individual. The NIS and KID do not capture outpatient procedures (TCD), medications (hydroxyurea), or transfusion history. The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study.

Subject Identification

Due to concern that the accuracy of ICD-9CM coding for specific forms of sickle cell disease (SCD), including SS, would be limited, discharges of interest were identified by ICD-9CM code for any form of SCD, including sickle beta thalassemia without crisis (282.41), sickle beta thalassemia with crisis (282.42), unspecified SCD (282.60), SS without crisis (282.61), SS with crisis (282.62), sickle hemoglobin-C disease without crisis (282.63), sickle hemoglobin-C disease with crisis (282.64), other SCD without crisis (282.68), and other SCD with crisis (282.69). Among discharges for children with SCD < 18 years old, stroke was identified using the ICD-9CM codes for subarachnoid hemorrhage (430), intracerebral hemorrhage (431), ischemic stroke (434.x), and acute cerebrovascular disease (436), consistent with prior research [18]. SCD codes were included whether the code was in the primary or any of 14 secondary discharge ICD-9CM code positions, whereas stroke codes were included only if in the first three ICD-9CM code positions, again consistent with prior research [18]. No significant changes in ICD-9CM coding practice occurred from 1993 to 2009 for either SCD or stroke. Exclusion criteria consisted of the use of the ICD-9CM codes for sickle cell trait (282.5), intracranial venous sinus thrombosis (325.x), stenosis of the pre-cerebral arteries (433.x), transient cerebral ischemia (435.x), other/ill-defined cerebrovascular disease (437), or late effects of cerebrovascular disease (438).

Definitions and Measurements

Variables—In-hospital mortality was coded as a binary variable, as provided by the NIS. Length of stay (LOS) in days was coded as a continuous variable. Hospital charges were obtained from the NIS in whole dollars. To account for inflation from 1993 to 2009, all charges were adjusted to 2009 dollar estimates using the Medical Care Index of the Consumer Price Index. Patient age and gender were obtained from distinct data elements in the NIS. Patients' insurance coverage was coded using the expected primary payer: Medicare, Medicaid, private insurance, self-pay, no charge, or other.

National estimates for SCD prevalence—Two recent national estimates of the prevalence of SCD in childhood in the year 2005 were identified [19,20]. The prevalence estimates from Hassell [20] were used in the primary analysis, and estimates from Brousseau et al. [19] were used in a sensitivity analysis. Relative population changes in the US Census for children 0–18 years old classified as “black alone or in combination” were then utilized to estimate the annual prevalence of SCD in the US from 1993 to 2009. For example, US census data document that the number of children classified as “black alone or in combination” increased by 0.45% from 2005 to 2006, so the number of children with SCD in 2006 was estimated by increasing the 2005 prevalence estimates by 0.45%. These annual prevalence estimates were then used to calculate the annual incidence of hospitalization for stroke.

Outcomes—The primary outcome was the secular trend in the annual incidence of hospitalization for stroke in children with SCD. Secondary outcomes included secular trends in cumulative hospital days for stroke cases, cumulative hospital charges secondary to stroke, and the median age of stroke cases.

Analyses

Descriptive statistics were used to compare SCD discharges with stroke to those without. National estimates for annual incidence rates of hospitalization for stroke were made using weights in the NIS and KID. Standard error calculations for national estimates were made using the method recommended by the NIS and KID [21]. The annual prevalence of hospitalizations for stroke was estimated from the NIS databases and used for all analyses, whereas estimates from KID were used as a comparator to NIS estimates. We analyzed the KID in addition to the NIS because stroke is a rare event and the KID includes about three times as many pediatric hospitalizations. If the NIS and KID estimates were similar for the years the KID was available, it would increase our confidence in the use of the NIS for the entire study frame.

We used simple linear regression to analyze the primary outcome of secular trends in incidence rate of hospitalization for stroke. Additionally, we compared the annual incidence rate of stroke for the years 1993–1998 and 1999–2009 with the Wilcoxon rank-sum test. These time periods were compared because, in 1998, STOP trial results were published and HU was licensed. Secular trends in secondary outcomes were also evaluated using simple linear regression. Secondary outcomes for the years 1993–1998 and 1999–2009 were compared with the Wilcoxon rank-sum test. All analyses were performed using SAS 9.2 (SAS, NC).

RESULTS

From 1993 to 2009 in weighted national estimates from the NIS databases, 2,024 discharges were identified for stroke in children with SCD. Sickle cell anemia (282.61 or 282.62) was coded for 63% of identified discharges. Another 34% of discharges had unspecified sickle cell disease (282.60). ICD-9CM codes for stroke were in the first code position in 65%, the second code position in 26%, and the third code position in 9% of identified discharges. ICD-9CM coding for stroke showed 65% of discharges with occlusion of the cerebral

arteries with infarction (434.x), 19% with acute cerebrovascular disease (436), 13% with subarachnoid or intracerebral hemorrhage (430 and 431), and 3% with two stroke codes.

Comparison of the demographic features and outcomes for hospitalizations with stroke ($N = 2,024$) versus all other SCD hospitalizations ($n = 542,386$) revealed that children for stroke had a hospitalized higher case fatality rate, increased LOS, and higher hospital charges (Table I). No difference was observed in age, gender, or the expected primary payer between stroke and all other SCD hospitalizations.

From 1993 to 1998 (pre-STOP), the mean annual incidence of hospitalization for stroke in the NIS was 0.51/100 patient years (95% confidence interval [CI], 0.41–0.60) which decreased by 45% to 0.28/100 patient years (95% CI, 0.23–0.33) from 1999–2009 ($P = 0.008$; Fig. 1). In the NIS, the lowest annual incidence rates of hospitalization for stroke occurred in 2006 (0.13/100 patient years [95% CI, 0.04–0.22]). Using mean annual incidence rates from 1993 to 1998 as the baseline, the decreasing trend in hospitalization for stroke was statistically significant (point estimate = $-0.022/100$ patient years [95% CI, -0.039 to -0.005], $P = 0.027$). In a sensitivity analysis, we used the SCD prevalence estimate from Brousseau et al. [19] instead of those from Hassell [20] and observed minimal differences in incidence rate point estimates (data not shown). Estimates from KID were similar to the NIS (Table II), with an incidence of 0.51/100 patient years (95% CI, 0.34–0.67) in 1997 which decreased by 45% to an average of 0.28 (95% CI, 0.20–0.37) for the years 2000, 2003, 2006, and 2009.

The mean annual cumulative hospital days attributable to stroke decreased 45% from 1,330 days/year (95% CI, 974–1,685) from 1993 to 1998 to 732 days/year (95% CI, 537–927) for 1999–2009 ($P = 0.004$; Fig. 2). Using the mean for 1993–1998 as the baseline, the difference in cumulative hospital days showed a trend toward statistical significance (point estimate = -51.7 days/year [95% CI, -105.1 to 1.7], $P = 0.086$). The mean annual cumulative hospital charges attributable to stroke decreased 24% from \$6.6 million/year (95% CI, 4.6–8.6) for 1993–1998 to \$5.0 million/year (95% CI, 3.7–6.3) for 1999–2009, although the difference was not statistically significant ($P = 0.21$). Using the mean for 1993–1998 as the baseline, the trend toward decreasing cumulative hospital charges was not statistically significant (point estimate = $-\$0.12$ [95% CI, -0.51 million, 0.27 million], $P = 0.57$). Finally, the secular trends in the median age of stroke did not change from 1993–1998 to 1999–2009 at 8.5 and 8.6 years, respectively.

DISCUSSION

In the first national estimates of hospitalization for stroke in children with SCD before and after the publication of the efficacy of primary stroke prevention, as well as hydroxyurea licensure, we show a twofold reduction in the annual incidence rate of hospitalizations for stroke. The decrease in the incidence of hospitalization for stroke is accompanied by a 45% reduction in total hospital days and a 24% reduction in total hospital charges attributable to stroke, although the latter was not statistically significant. We assume that the majority of the reduction in hospitalization for stroke in the United States is due to primary stroke

prevention, because the magnitude of benefit of HU is not established, and it appears to be less efficacious than primary stroke prevention [22].

Two prior studies have examined changes in the epidemiology of stroke before and after the use of primary stroke prevention and HU. In a study of a single, large academic center in Philadelphia, the incidence rate of stroke decreased 91% from 0.67/100 patient years to 0.06/100 patient years in the 8 years following institution of primary stroke prevention, compared to the preceding 8 years [16]. The only study of a larger population analyzed data from the state of California from 1991 to 2000. An 80% decline in the rate of stroke was observed, from 0.88/100 patient years from 1991 to 1998 to 0.17/100 patient years in 1999–2000 [17]. Several factors likely contribute to differences in stroke rate reductions between our estimates and those previously reported. Most importantly, we have performed a national study, as opposed to prior regional studies. For the single center study, it would be expected that stroke reduction would be enhanced by the resources, personnel, and expertise that are available in a large academic center. For the study of California from 1991 to 2000, northern California is home to a large sickle cell center that participated in the STOP trial, and therefore, may have been uniquely prepared to quickly institute primary stroke prevention and affect a rapid change in stroke rates. Also, our study revealed a marked decrease in 1999 and 2000 (63%) in national incidence rates of hospitalization for stroke which was not representative of the larger trend over time. This early, large decrease might also be attributable to aggressive initial screening of the highest-risk individuals or chance.

Previous research on stroke incidence rates before routine use of primary stroke prevention and HU provided estimates of 0.61 [1], 0.67 [16], 0.76 [2], 0.85 [23], and 0.88 [17] per 100 patient years. At least three factors may contribute to the difference between these and our baseline estimate of 0.51 per 100 patient years. First, the denominator used in our incidence calculation included all SCD genotypes. Mild SCD genotypes (sickle hemoglobin-C disease and sickle β^+ thalassemia) account for 30–35% of all SCD but have a much lower associated risk of stroke than severe genotypes. Decreasing the denominator in our estimates by 30–35%, to include only those with SS or sickle β^0 thalassemia, yields estimates comparable to previous studies. Second, we used an approach to case identification with ICD-9CM codes that enhanced specificity, and thereby, sacrificed some sensitivity. This approach had a specificity of 99.8% and a sensitivity of 74% in adults with SCD and stroke [18] and likely decreased our incidence estimate. Finally, by examining an inpatient database for stroke, the assumption is made that all cases of stroke are admitted to the hospital. This assumption may not be valid, depending on the timing of presentation and the neurologic status of a patient (e.g., a patient who 1 week ago had 3 days of arm weakness but now presents with a nearly normal neurologic exam could conceivably not be admitted to the hospital in some practices but simply started on transfusions as an outpatient). Nevertheless, this factor should have varied randomly and minimally over time and would not invalidate our findings of secular trends in stroke as identified in HCUP databases.

Several factors may contribute to the ongoing stroke burden for US children with SCD, including barriers to TCD screening and poor adherence to serial TCD screening. In a 2006 physician survey, patient non-adherence (missed appointments) was the most frequently cited barrier (72%) to TCD screening. Distance to a TCD center (22%), lack of insurance

authorization (13%), low patient cooperativeness (13%), and unavailability of TCD (11%) were also cited as barriers to TCD screening [24]. Semi-structured interviews of 36 caregivers of children with SCD revealed lack of knowledge, low self-efficacy, and fear of chronic transfusions as the most commonly reported barriers to TCD screening [25]. Availability of TCD screening, transportation, and financial difficulties were among the practical barriers infrequently cited by SCD caregivers. In a retrospective, single-center study from 2008, the average yearly screening rate for TCDs was low, at 45% [26]. Compared to patients with Medicaid, patients with private insurance were three times more likely to attend an annual TCD screening, and patients who attended hematology clinic visits were more likely to attend an annual TCD screening. Taken together, these studies suggest that interventions aimed at increasing caregiver knowledge about TCDs and increase adherence to TCD appointments may improve TCD screening rates, and thereby, further decrease the stroke incidence rate. Importantly, the incidence rate of hospitalization for stroke does not appear to have stabilized, which suggests that the incidence of stroke may still be decreasing.

Several study limitations should be noted. First, the databases used for this analysis are de-identified, so it is not possible to confirm, through review of medical records, the presence of acute stroke in any of these hospitalizations. It is, therefore, possible that some of the identified discharges were not for stroke but for other medical problems. The identification technique used for this study has been evaluated, including medical record review, in other populations and demonstrated very high specificity (as above) but has not been examined in the pediatric SCD population. Additionally, primary stroke cannot be differentiated from recurrent stroke in these administrative databases. Recurrent strokes have been described to occur in 20% of patients on chronic transfusions for secondary stroke prevention [27]. The proportion of all strokes accounted for by recurrent strokes is unknown. We speculate that the stroke recurrence rate has been stable over time in the SCD patient population, and inclusion of recurrent strokes would underestimate the decrease in primary stroke rates. Additionally, we cannot assess the medication history or adherence to primary stroke prevention for patients in the NIS and KID databases. Finally, the relationship of incidence rates of hospitalization for stroke with the timing of the STOP trial publication and hydroxyurea licensure is strictly temporal, so causation cannot be assumed.

In conclusion, this study is the first to estimate national secular trends in incidence rates of hospitalization for stroke in children with SCD. Decreases in incidence rates of hospitalization for stroke suggest that primary stroke prevention uptake and utilization have occurred broadly, but the residual burden of stroke indicates that continued efforts are needed to improve the availability of and adherence to primary stroke prevention. A registry of stroke in SCD patients after institution of primary stroke prevention would greatly contribute to identification of factors associated with the remaining stroke burden.

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Fig. 1.

National trend in annual incidence rates of hospitalization for stroke in US children with sickle cell disease. Prior to STOP trial publication and hydroxyurea licensure (1993–1998), the mean annual incidence rate of hospitalization for stroke was 0.51 per 100 patient years. Following STOP trial publication and hydroxyurea licensure (1999–2009), the mean annual incidence rate of hospitalization for stroke decreased 45% to 0.28 per 100 patient years.

Fig. 2.

National trend in annual cumulative hospital days for stroke in US children with sickle cell disease. The mean annual cumulative hospital days attributable to stroke decreased 45% from 1,330 days/year (95% CI, 974–1,685) from 1993 to 1998 to 732 days/year (95% C.I., 537–927) for 1999–2009.

TABLE I

Comparison of Hospitalizations for Stroke Versus All Other Conditions in US Children With SCD*

Characteristic	Stroke (N = 2,204)	All other SCD hospitalizations (N = 542,386)
Age, years, median (IQR)	8 (5–13)	9 (3–14)
Female (%)	46	48
Primary payer (%)		
Medicaid	60	66
Private/HMO	30	28
Self-pay	3	3
Died (%)	3.2	0.1
Length of stay, days, median (IQR)	5 (3–9)	3 (2–5)
Charges, \$ × 10 ³ , median (IQR)	18.3 (9.6–35.5)	6.5 (3.8–11.9)

SCD, sickle cell disease; IQR, inter-quartile range.

* No statistical tests comparing stroke and all other SCD hospitalizations were performed, due to the very large sample size of the all other SCD group.

TABLE II

Comparison of Stroke Incidence Rates in the NIS and KID Databases Among US Children With SCD

Year	Stroke incidence—NIS databases (stroke/100 patient years with 95% CI)	Stroke incidence—KID databases (stroke/100 patient years with 95% CI)
1997	0.54 (0.32, 0.76)	0.51 (0.34, 0.67)
2000	0.19 (0.07, 0.31)	0.33 (0.22, 0.44)
2003	0.23 (0.09, 0.36)	0.32 (0.22, 0.43)
2006	0.13 (0.04, 0.22)	0.25 (0.16, 0.34)
2009	0.24 (0.08, 0.39)	0.28 (0.20, 0.37)

NIS, nationwide inpatient sample; KID, kids' inpatient database; SCD, sickle cell disease; CI, confidence interval.