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ORIGINAL RESEARCH

Transfusion Practice

TRANSFUSION

Longitudinal outcomes of chronically transfused adults with sickle cell disease and a history of childhood stroke

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Abstract

Background: Many children with sickle cell disease (SCD) who suffer a stroke receive chronic transfusion therapy (CTT) indefinitely; however, their adulthood neurologic outcomes have not been reported. Understanding these outcomes is critical to inform decisions regarding curative therapy in childhood.

Study Design and Methods: In this retrospective study, we described a cohort of adults with SCD and a history of childhood stroke who received care at a single center and compared their outcomes with matched subjects without childhood stroke using chi^2 and Mann–Whitney *U* tests.

Results: Of 42 subjects with childhood stroke, all received CTT for secondary stroke prophylaxis. Five (11%) developed recurrent stroke. The rate of stroke was similar in subjects with and without childhood stroke (0.7 vs. 1.1 per 100 person·years, $p = .63$). Both cohorts exhibited evidence of iron overload (median ferritin 2227 vs. 1409 ng/dL, $p = .10$) and alloimmunization (45% vs. 45%, $p = 1.0$), despite receiving care in a comprehensive SCD program.

Discussion: For adults with SCD who had a childhood stroke, our results suggest CTT returns the risk of stroke to that of age-matched stroke naïve patients with SCD.

KEYWORDS

cerebrovascular accident, chronic red cell exchange transfusions, sickle cell disease, therapeutic apheresis

1 | INTRODUCTION

The prevalence of stroke in sickle cell disease (SCD) was 11% in children prior to widespread adoption of transcranial doppler (TCD) screening and chronic transfusion therapy (CTT).[1] These practices were validated by the clinical trials STOP I and II, which demonstrated a 92% reduction in overt stroke risk in children with abnormal

Abbreviations: ANC, absolute neutrophil count; ASH, American Society of Hematology; CTA, computed tomography angiography; CTT, chronic transfusion therapy; EMR, electronic medical record; HRQOL, health-related quality of life; IQR, interquartile ranges; MRA, magnetic resonance angiography; SCD, sickle cell disease; TCD, transcranial doppler; TRJV, tricuspid regurgitant jet velocity.

TCDs who started and remained on CTT.[2,3] Randomized data have also demonstrated superiority of CTT over hydroxyurea to prevent recurrent strokes in children with a history of overt stroke.[4] Based on these trials, the National Heart Lung and Blood Institute recommends initiation of a monthly simple transfusion or chronic exchange program for children and adults with a history of overt stroke.[5] More recently, the American Society of Hematology (ASH) recommended CTT for children with SCD and a history of overt stroke. ASH makes no recommendation regarding continuation of CTT beyond childhood for secondary stroke prevention because randomized trials to address stroke risk or prevention for adults with SCD have not been performed.[2–4,6,7] In fact, the clinical outcomes for patients with a history of childhood stroke who survive to adulthood have not been rigorously studied.[8] It is unclear if the benefits of indefinite CTT justify the burden and risk in this population. Long-term CTT causes physical adverse effects, such as complications from vascular access, alloimmunization, and iron overload.[9,10] Furthermore, a time-consuming monthly therapy may compound social pressures (e.g., school, employment), as described by parents of children who receive CTT.[11,12] Committing a patient to indefinite CTT is consequential. Therefore, understanding the clinical outcomes of adults with a history of childhood stroke is of critical importance.

The purpose of this retrospective study was to describe the neurologic outcomes of adults with SCD and a history of childhood stroke, cared for longitudinally at a single center with comprehensive pediatric and adult SCD programs. We compared outcomes of this adult population to matched controls with no history of childhood stroke who received a similar duration of continuous, comprehensive SCD care. We hypothesized that CTT continues to prevent recurrent stroke in adulthood and may confer protection from other SCD-related end-organ damage.

2 | METHODS

The Johns Hopkins University Institutional Review Board approved this study.

The inclusion criteria for all subjects were: age ≥18 years, diagnosis of HbSS or HbSβ^0, and in care at the Johns Hopkins Medical Institutions (JHMI) which includes Bloomberg Children's Center and the Johns Hopkins Sickle Cell Center for Adults. Subjects could be in pediatric or adult care at the time of study inclusion since the typical age at transfer to adult care is 22 years. Subjects were included in the "childhood stroke" cohort if they had documentation of a hemorrhagic or ischemic stroke before 18 years in a Hematology note. Subjects were included in the "without childhood stroke" cohort if they did not have a documented hemorrhagic or ischemic stroke before 18 years. Subjects with silent cerebral infarctions were excluded because these were not detected or documented consistently in the medical record. Subjects under the age of 18 years were excluded. Subjects with and without childhood stroke were matched based on age, gender, and genotype.

We utilized three methods to generate a complete list of eligible subjects. First, we queried the electronic medical record (EMR) for all subjects with the ICD 10 codes, or ICD 9 code equivalents, for "Sickle-cell disorders" (D57) and "Cerebral infarction" (I63), "History of cerebrovascular disease without any sequelae or late effects" (Z86.73), or "Nontraumatic intracerebral hemorrhage, unspecified" (I61.9). Then, we queried "Sickle-cell disorders" alone to generate a list of potential matched subjects without a history of childhood stroke. Second, we reviewed the list of all subjects with SCD receiving CTT at our institution. Third, we identified all subjects with the CPT code for "Transcranial Doppler Study of the Intracranial Arteries; Complete Study" (93886). We screened each subject for eligibility and retained those that met inclusion criteria.

For each subject, we performed a chart review from the first pediatric or adult visit at JHMI (whichever was available) to the last available adult or pediatric visit in the EMR. We reviewed records dated January 1990 to February 2022. We evaluated stroke history using several variables. For subjects with a history of adult or pediatric stroke, we recorded the date of the stroke, whether the patient was on CTT or hydroxyurea before the stroke and if on CTT, whether the patient attended all transfusion sessions 3 months before the stroke. If the subject was prescribed hydroxyurea, the admission absolute neutrophil count (ANC) was captured. ANCs of 2000–4000/μL suggested that the subject was taking hydroxyurea at maximally tolerated doses. For all study subjects, we evaluated available brain magnetic resonance angiography (MRA), and computed tomography angiography (CTA) reports for mention of Moya Moya Syndrome, stenoses, or aneurysms. Any subjects with these findings were recorded as having "evidence of vasculopathy."

We documented basic demographic data, presence of SCD specific comorbidities, and SCD disease modifying therapies. SCD comorbidities included: priapism, acute chest syndrome, inherited and acquired hypercoagulable states, thrombosis, chronic kidney disease Stage I and greater, elevated tricuspid regurgitant jet velocity (TRJV), avascular necrosis, gallbladder disease, leg

ulcers, obstructive sleep apnea, retinopathy, hypertension, diabetes, and alloimmunization. Disease modifying therapies included hydroxyurea, L-glutamine, voxelotor, crizanlizumab, CTT, and bone marrow transplant. If available, we recorded the specific modality of CTT used: simple transfusion/partial manual exchange or automated exchange.

All subjects with a history of stroke are encouraged to remain on CTT for secondary stroke prophylaxis due to a lack of data to support a safe and effective alternative. At our institution, all subjects referred for CTT as secondary stroke prophylaxis have a goal pre-procedure hemoglobin S%(HbS) of 30%. For this study, adherence was defined as attendance at 60% or more of scheduled 3–4 weekly transfusions (simple/partial manual exchange or automated exchange) with 6 or fewer months between transfusions. We used this liberal definition of treatment adherence because discontinuation of therapy for short periods may still offer some protection against recurrent stroke.[4]

Lastly, we recorded the last ambulatory ferritin value of each year reviewed if the subject had ever received a prescription for iron chelation, and current or history of alloimmunization. We used these as surrogates for an iron overload diagnosis. ASH recommends annual iron overload screening with magnetic resonance imaging R2, R2*, or T2* over serial ferritin levels[13]; however, these studies were not routinely performed and could not be evaluated in a systematic way. Our practice is to initiate iron chelation therapy if the ferritin is > 1000 ng/dL and if an MRI Liver T2* was performed, the liver iron concentration is > 5 mg/g. Alloimmunization data were recorded from the blood bank laboratory information system. In our healthcare system, patients do not receive prophylactically Rh-Kell matched red cell units. Once an alloantibody develops, the patient receives red cell units matched for the extended red cell phenotype (i.e. ABO, Rh, Kell, Kidd, Duffy, Ss).

2.1 | Statistical analysis

We performed basic descriptive statistics on the cohort of subjects with a history of childhood stroke. Medians and interquartile ranges (IQR) are reported for all nonparametric data. We compared subjects with and without a history of childhood stroke using the Mann–Whitney *U* test for continuous outcomes and Fisher's exact test for categorical outcomes. All *p* values were two-sided, and a *p* value $\leq .05$ was considered significant. We did not report 95% confidence intervals because the data are nonparametric. We analyzed data and performed all subject matching using Stata/SE Version 16.1.

3 | RESULTS

3.1 | History of childhood stroke cohort

Forty-two subjects with a history of childhood stroke met inclusion criteria. Cohort demographics are presented in Table 1: Half were female, 98% had HbSS, and the median age was 30 years (IQR 24–35 years). The median age at the time of first stroke was 7 years (IQR 5–11). Two subjects (5%) were deceased: one at age 35 due to intracranial hemorrhage and the other at age 42 due to sepsis. One subject was lost to follow-up at age 18 years.

All subjects received CTT for at least 6 months following their childhood stroke. The median time on CTT was 17.7 years (IQR 12.2–23.3 years). The adherence to CTT was 98% (IQR 58%–100%), with 80% of subjects demonstrating 100% adherence, as defined above. Many subjects received both simple transfusions/partial manual exchanges and automated exchanges for CTT. The median proportion of simple

TABLE 1 Adult subjects with sickle cell disease and a history of overt stroke in childhood ($n = 42$).

Female gender (%)	21 (50)
Median age, years (IQR)	30 (24–35)
Genotype (%)	
SS	41 (98)
$S\beta^0$	1 (2)
Race	
African or African American	41 (98)
Other	1 (2)
Median years in adult care (IQR)	4 (1–9)
Deaths (%)	2 (5)
Lost to follow-up (%)	1 (2)
Diagnosed with stroke in adulthood (%)	5 (12)
Median age at time of childhood stroke, years (IQR)	7 (5–11)
Treated with CTT (%)	42 (100)
Median years on CTT (IQR)	17.7 (12.2–23.3)
Adherence rate to CTT (%, IQR)	98 (58–100)
Median % of CTT procedures simple transfusion and partial manual exchange (IQR)	62 (10–95)
Median % of CTT procedures automated exchange (IQR)	38 (5–90)
Mean ferritin, ng/dL (SD)	3842 (3420)
Alloimmunized (%)	19 (45)

TABLE 2 Description of subjects with a history of childhood stroke at the time of adulthood stroke.

Subject	Age (years)	Imaging evidence of cerebral vasculopathy	Disease modification	Relevant admission laboratory studies
1	24	Yes[a]	Hydroxyurea	Absolute neutrophil count: 5820/μL Mean corpuscular volume: 75.5 fL Hemoglobin F: 3.3%
2	21	Yes	Hydroxyurea	Absolute neutrophil count: 13,113/μL Mean corpuscular volume: 96.3 fL Hemoglobin F: 9.9%
3	22	No	Hydroxyurea	Absolute neutrophil count: 12,408/μL Mean corpuscular volume: 95.9 fL Hemoglobin F: 0%
4	23	Yes[a]	CTT	Hemoglobin: 7.4 g/dL Hemoglobin S: 49.4% (Mean pre-procedure hemoglobin S: 17%)
5	21	Yes	CTT	Hemoglobin 8.2 g/dL Hemoglobin S: 14.2% (Mean pre-procedure hemoglobin S: 12%)

[a]Diagnosed with Moya Moya Syndrome.

transfusions or partial manual exchanges was greater than automated exchanges for each subject's CTT regimen (62% vs. 38%).

Five subjects (11%) with a history of childhood stroke had a stroke in adulthood; all occurred between ages 21 and 24 years and most ($n = 4$) had cerebral vasculopathy by MRA (Table 2). Overall, three subjects with recurrent stroke took hydroxyurea and two continued on CTT. At the time of stroke admission, all three subjects taking hydroxyurea had absolute neutrophil counts greater than 4000/μL and hemoglobin F percentages <10%, suggesting that no subject was at maximally tolerated dose or experiencing an effective response to hydroxyurea. All three subjects had received CTT after their childhood stroke but had transitioned to hydroxyurea prior to their recurrent adult stroke. The interval between discontinuation of CTT and adulthood stroke was 3 months for Subject 2 and 38 months for Subject 3. This interval is unknown for Subject 1 due to missing data from the EMR. The remaining two subjects were on CTT at the time of adulthood stroke. One subject was non-adherent to CTT and presented with a HbS of 49.4% and hemoglobin of 7.4 g/dL. The subject who was adherent to CTT presented with a HbS of 14.2% and hemoglobin of 8.2 g/dL. Among subjects with cerebral vasculopathy, two were prescribed hydroxyurea and two CTT. No subjects had been diagnosed with traditional stroke risk factors, such as hypertension or type 2 diabetes.

3.2 | Matched cohort analysis

Thirty-three of 42 subjects (79%) with a history of childhood stroke were matched with control subjects with no history of childhood stroke. Nine subjects were excluded due to lack of available age, gender, and genotype matched subjects. Characteristics of the matched cohort are shown in Table 3.

Subjects with and without a history of childhood stroke were followed in the adult clinic for a median of 5 person-years (IQR 1 to 9) and 3 person-years (IQR 1 to 10), respectively. Compared to subjects with no history of childhood stroke, more subjects with a history of childhood stroke received CTT (33 vs. 21, $p = .000$), started CTT at a younger age (6 vs. 23 years old, $p = .000$), and remained on therapy for a longer time (19.4 vs. 6.8 years, $p = .000$). CTT for subjects without a history of childhood stroke more often comprised automated exchanges than simple transfusions or partial manual exchanges (54% vs. 46%). The indications for CTT in the control cohort are given in Table S1.

There was no between-group difference in the rate of adulthood stroke events per 100 person-years (0.7 vs. 1.1, $p = .63$) or age at the time of adulthood stroke (23 vs. 25 years, $p = .57$). Cerebral vasculopathy on computed tomography or MRI was more common in subjects with a history of childhood stroke than in those without (22 vs. 5, $p < .001$). Of subjects without a history of childhood stroke who developed an adulthood stroke ($n = 5$),

TABLE 3 Sickle cell outcomes in subjects with and without a history of childhood stroke ($n = 66$).

	History of stroke ($n = 33$)	No history of stroke ($n = 33$)	p
Female gender (%)	18 (55)	18 (55)	1.0
Median age, years (IQR)	29 (24–34)	30 (24–35)	1.0
Genotype (%)			
SS	32 (97)	32 (97)	1.0
$S\beta^0$	1 (3)	1 (3)	–
Race (%)			
African or African American	32 (97)	31 (94)	1.0
Other	1 (3)	2 (6)	–
Total person-years in adult care	187	197	–
Median person-years in adult care (IQR)	5 (1–9)	3 (1–10)	.90
Deaths (%)	2 (6)	1 (3)	1.0
Lost to follow-up (%)	1 (3)	0	1.0
Received CTT (%)	33 (100)	21 (63)	.000*
Median years on CTT (IQR)	19.4 (13.75–23.8)	6.8 (1.53–13.53)	.000*
Median age at CTT start, years (IQR)	6 (4–11)	23 (18–30)	.000*
Median % of CTT procedures simple transfusion and partial manual exchange (IQR)	64 (28–92)	46 (12–100)	.90
Median % of CTT procedures automated exchange (IQR)	36 (8–71)	54 (0–88)	.90
Hydroxyurea use (%)	12 (36)	30 (91)	.000*
Median years on hydroxyurea (IQR)	3.5 (2–6.5)	4.5 (3–7)	.31
L-glutamine (%)	0	2 (6)	.49
Voxelotor (%)	0	3 (9)	.24
Crizanlizumab (%)	0	1 (3)	1.0
Adulthood stroke events per 100 person-years	0.7	1.1	.63
Total adulthood strokes (%)	3 (9)[c]	5 (15)	.71
Age at the time of adulthood stroke (IQR)	23 (21–24)	25 (22–28)	.57
Median hospitalizations in adulthood per 10 person·years (IQR)	8 (3 to 17)	10 (6 to 16)	.3
Presence of vasculopathy (%)[a]	22 (67)	5 (15)	.000*
Hematopoietic stem cell recipient (%)[b]	1 (3)	1 (3)	–

*$p < .05$.
[a]Number of imaging studies to evaluate for cerebral vasculopathy was similar between the two groups (30 vs. 25, $p = .19$).
[b]Both HSCT recipients are currently engrafted.
[c]Two of the 9 unmatched subjects with a history of childhood stroke had an adulthood stroke. Excluding these subjects resulted in a reduction in the incidence of adulthood stroke from 11.9% to 9% in this cohort.

two had vasculopathy on imaging and one had traditional ischemic stroke risk factors (hypertension, coronary artery disease). The etiology for adulthood stroke in the remaining two subjects was unclear from the EMR.

Additional SCD comorbidities were assessed. Subjects with a history of childhood stroke had less avascular necrosis (4 vs. 14, $p = .01$) and leg ulcers (0 vs. 6, $p = .02$) (Figure 1). There was a trend toward less chronic kidney disease among subjects with a history of childhood stroke (14 vs. 21, $p = .13$). There were no other differences in SCD specific comorbidities between the cohorts. Further, there were no between-group differences in median hospitalizations in adulthood per 10 person years (8, IQR 3 to 17 vs. 10, IQR 6 to 16, p=0.3) (Table 3).

Both cohorts experienced alloimmunization and iron overload. There was no between-group difference in the prevalence of alloimmunization (16 vs. 16) or in alloantibody distribution between Rh and non-Rh alloantibodies (Table S2, $p = .33$). Subjects with a history of childhood stroke had a trend toward higher median annual ferritin

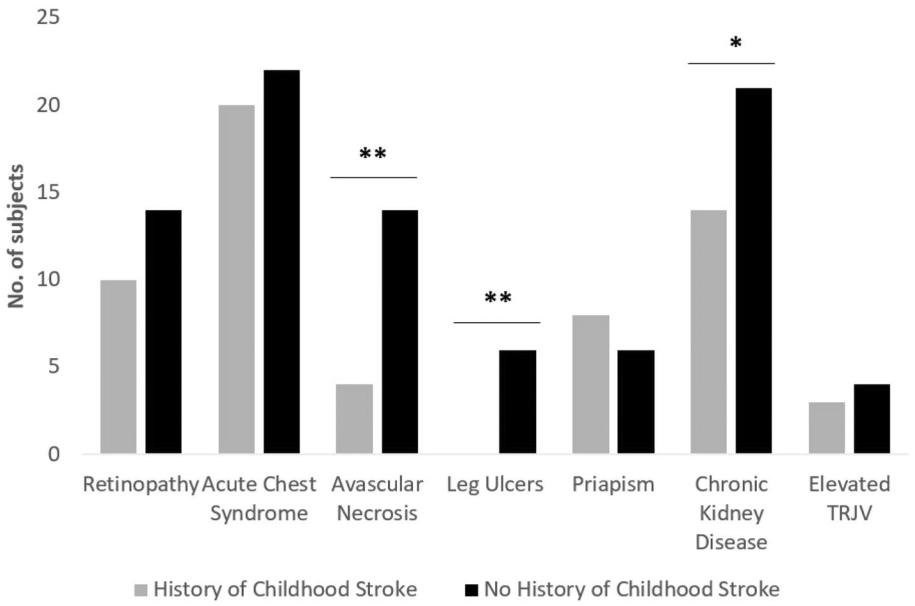

FIGURE 1 Prevalence of sickle cell disease (SCD) comorbidities in subjects with and without a history of childhood stroke. The prevalence of avascular necrosis (4 vs. 14, $p = .01$) and leg ulcers (0 vs. 6, $p = .02$) was lower in subjects with a history of childhood stroke as compared to subjects without. The prevalence of chronic kidney disease (Stage I or greater) trended lower in subjects with a history of childhood stroke (14 vs. 21, $p = .13$). Differences in the prevalence of other SCD comorbidities (retinopathy, acute chest syndrome, priapism, chronic kidney disease, elevated tricuspid jet velocity [TRJV]) between the cohorts were not observed.

(2227 ng/dL, IQR 785–5770 vs. 1409 ng/dL, IQR 175–3591, $p = .10$), and this group was more often prescribed iron chelation (29 vs. 18, $p = .003$).

4 | DISCUSSION

In this retrospective cohort study, five subjects (11%) with a history of childhood stroke had a recurrent stroke in adulthood, most had cerebral vasculopathy, and one was at the target hemoglobin S of <30% on CTT. Subjects with a history of childhood stroke had fewer leg ulcers and avascular necrosis. In this pilot study, stroke risk in those with a history of childhood stroke on CTT is the same as the general adult sickle cell anemia (hemoglobin SS and hemoglobin $S\beta^0$) population.

Here, CTT appears to protect against recurrent stroke in high-risk adults with SCD; 37 out of 42 subjects (88%) with a history of childhood stroke did not have a recurrent stroke in adulthood. The true risk of recurrent stroke for adults with SCD and a history of childhood stroke who have remained on CTT is unknown. Observations from the CSSCD suggest a stroke recurrence rate of 6.4 per 100 person-years for patients with first stroke before age 20 and 1.6 per 100 person-years for patients with first stroke after age 20.[1] However, these data predate the use of transcranial doppler screening and primary and secondary CTT to prevent childhood stroke. In a more contemporary study, when CTT was widely utilized to prevent first time stroke in children with abnormal transcranial doppler studies, the incidence of first time stroke in 18–34 year olds with SCD was 0.36 per 100 person-years and in adults over 35 years was 1.16 per 100 person-years.[6,14] The incidence of recurrent stroke in our study was between these values at 0.7 per 100 person-years, suggesting that CTT may reduce the risk of stroke to that of stroke naïve adults with SCD. However, the risk of stroke in adults with SCD remains higher than that of the general non-SCD population and still contributes to significant morbidity for adults with SCD.[15]

Clinicians, patients, and family consider indefinite CTT versus curative therapy for individuals with SCD complicated by stroke.[16] Our results suggest that adherence to CTT for patients with a history of stroke is necessary for secondary stroke prevention; however, even with optimal transfusion adherence patients are at risk for recurrent stroke. Strict adherence to monthly treatment may present unique challenges that change across the lifespan. In adulthood, competing pressures from family, employment, and other personal circumstances may affect adult treatment choices and adherence.[17–19] Health-related quality of life (HRQOL) for adults with SCD on CTT has not been studied, but pediatric studies indicate that CTT is burdensome for patients and their families.[17,18,20] Thus, indefinite CTT may not be the preferred secondary stroke prophylaxis strategy. In contrast, curative therapies, when successful, may lead to minimal disruption in adult lives.[21] Outcomes after transplant for children with SCD and cerebrovascular disease demonstrate low stroke rates and improvement in underlying cerebrovascular pathology.[22–25] Patients also report improved HRQOL.[21] However, curative therapies are associated with significant risks, such as severe infections, infertility, and graft versus host disease in allogeneic bone marrow transplants, which should be thoroughly discussed with interested patients and their families.

Indefinite CTT is also associated with adverse effects. Iron overload and alloimmunization are well-described complications of CTT. Iron overload causes significant morbidity and is associated with early mortality.[10,26–28] In this cohort, median annual serum ferritin was greater than 1000 ng/dL, consistent with iron overload in most subjects. Exchange transfusions can mitigate the effects of iron loading in some patients and are recommended by the American Society of Hematology.[9,13,29,30] At our institution, the typical automated exchange transfusion practice is to target an end hematocrit of 27%–30% and to avoid raising the hematocrit by >3%. Ferritin is measured at each automated exchange transfusion procedure. Patients with confirmed iron overload on MRI T2* receive iron chelation. Many subjects in our cohort had iron overload despite chelation therapy. Several factors may have contributed to the high prevalence of iron overload. These include prolonged simple transfusion or partial manual exchange use prior to transition to automated exchange, liberal simple transfusion practices at other healthcare where subjects may have sought care, nonadherence to chelation therapy, or ineffective chelation therapy.

Lifetime risk of alloimmunization is especially concerning for younger patients committed to indefinite CTT and for whom no other SCD therapy has demonstrated evidence. In our study, 45% of subjects were alloimmunized.[31] Alloimmunization is associated with an increased risk of delayed hemolytic transfusion reactions which can be fatal, delays in care due to difficulty identifying suitable red cell units and more costly care.[32–34] Extensive alloimmunization or alloimmunization to high frequency red cell antigens can jeopardize eligibility for curative therapy, if sufficient red cell units are not available to support the patient until engraftment.[35]

In lieu of curative therapies, hydroxyurea is an attractive alternative to CTT. Hydroxyurea is an affordable, oral, once-daily therapy with minimal side effects and therefore may be perceived as easier and safer to use than CTT by providers and patients. No randomized studies have compared the efficacy of hydroxyurea for secondary stroke prophylaxis directly with CTT in adults with SCD. A recent study by Abdullahi et al. suggest that the risk of recurrent stroke for children taking fixed dose (10–20 mg/kg/day) hydroxyurea may be modest compared to historical cohorts on CTT; however, these results may not be generalizable to adults with SCD. Observational studies have demonstrated recurrent strokes in children and young adults who transition from CTT to hydroxyurea.[4,36,37] Definitive risks of substituting hydroxyurea for CTT in this population are unknown. Extrapolation of the pediatric data would suggest that hydroxyurea provides inferior secondary stroke prophylaxis and should be considered second line therapy in patients with SCD and a history of stroke.

CTT may offer protection from SCD comorbidities beyond central nervous system disease. In our cohort, adults with a history of childhood stroke showed a reduced prevalence of avascular necrosis and leg ulcers compared to those without a history of childhood stroke. Avascular necrosis and leg ulcers cause chronic pain and drive acute care utilization in patients with SCD.[38,39] Effective preventative strategies for these specific complications are desperately needed but have remained elusive; even hydroxyurea has not demonstrated a protective effect.[40–43] Although our observations are encouraging, they must be confirmed with dedicated studies. Furthermore, future investigation should identify children at high-risk for the development of these non-stroke SCD complications who might benefit from primary prophylaxis with CTT.

This study's strengths include the length of long-term follow-up of subjects at a single institution. Several subjects, having received care at our institution from birth to adulthood, contributed over 20 years of data to our analysis. Ideally, prospective, multicenter results would be available to inform decisions about secondary stroke prophylaxis in adults with SCD, but randomized trials are unlikely to be performed due to concerns regarding equipoise. Therefore, observational studies may be the only means of answering these questions. Real-world studies from contemporary registries may provide additional data to confirm the outcomes described in this retrospective study.[44]

This study has limitations. First, the study was retrospective, so controlling for all potential confounders, such as evolution of screening practices for detection of end organ dysfunction, over the many years of follow-up was not possible. Second, subjects with and without a history of childhood stroke received CTT; therefore, we cannot conclude definitively that CTT prevented the described outcomes. Subjects with a history of childhood stroke began CTT at an earlier age and continued CTT for a longer period as compared to those without a history of childhood stroke. Furthermore, subjects with a history of childhood stroke were infrequently exposed to other disease modifying therapies. Consequently, we would expect CTT to have a much larger impact on the clinical outcomes of subjects with a history of childhood stroke compared to those without. We did not control for CTT during the matching process for two reasons: (1) it would have been unrealistic to find sufficient subjects without a history of childhood stroke who received a similar duration of CTT to match those with a history of childhood stroke, and (2) we would not expect a

cohort of subjects without a history of childhood stroke who had received CTT since childhood for non-stroke indications to be a representative sample of the general SCD population. Third, regular clinic visits may have contributed to improved clinical outcomes in subjects with a history of childhood stroke. Although both groups had similar adult care follow-up, subjects with a history of childhood stroke have had monthly contact with the clinical team since childhood. Regular follow-up provides more opportunities for addressing clinical complaints, practicing evidence-based screening studies, and communicating with patients in real time regarding important aspects of care (e.g., prescription refills and encouraging treatment adherence). Lastly, our record review may not have been comprehensive due to the switch from written to electronic records at our institution in 2003. The incorporation of written records into the electronic record was considered mostly complete, but we were unable to verify if any parts of the records were missing.

5 | CONCLUSION

Patients with SCD and a history of childhood stroke appear to benefit from continued CTT in adulthood. However, prolonged CTT is associated with a high prevalence of iron overload and alloimmunization, which may be harmful to patients in the long term. If available, curative therapy may offer patients the best opportunity for secondary stroke prophylaxis and prevention of other SCD-related end organ complications.

AUTHOR CONTRIBUTIONS

J.J. and S.L. conceived and designed the study. J.J. and J.W. collected and analyzed data. J.J., E.B., L.C., L.P., and S.L. prepared and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

For access to original data, please contact the corresponding author directly at jonjm@med.umich.edu.

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REFERENCES

1. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288–94.
2. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5–11.
3. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005;353(26):2769–78.
4. Ware RE, Schultz WH, Yovetich N, Mortier NA, Alvarez O, Hilliard L, et al. Stroke with transfusions changing to Hydroxyurea (SWiTCH): a phase III randomized clinical trial for treatment of children with sickle cell anemia, stroke, and iron overload. Pediatr Blood Cancer. 2011;57(6):1011–7.
5. Evidence-based management of sickle cell disease: expert panel. 2014: 161.
6. Adams RJ, Brambilla DJ, Granger S, Gallagher D, Vichinsky E, Abboud MR, et al. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. Blood. 2004;103(10):3689–94.
7. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554–88.
8. Neumayr L, Vichinsky E. Stroke recurrence in adult sickle cell patients: it is time for action! Transfusion (Paris). 2016;56(5):1001–4.
9. Fasano RM, Leong T, Kaushal M, Sagiv E, Luban NLC, Meier ER. Effectiveness of red blood cell exchange, partial manual exchange, and simple transfusion concurrently with iron chelation therapy in reducing iron overload in chronically transfused sickle cell anemia patients. Transfusion (Paris). 2016;56(7):1707–15.
10. Chou ST, Fasano RM. Management of Patients with sickle cell disease using transfusion therapy: guidelines and complications. Hematol Oncol Clin North Am. 2016;30(3):591–608.
11. Beverung LM, Strouse JJ, Hulbert ML, Neville K, Liem RI, Inusa B, et al. Health-related quality of life in children with sickle cell anemia: impact of blood transfusion therapy. Am J Hematol. 2015;90(2):139–43.
12. Maxwell SL, Schlenz AM, Kanter J. Health-related quality of life in children with sickle cell disease undergoing chronic red cell transfusion therapy. J Pediatr Hematol Oncol. 2019;41(4):307–12.
13. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327–55.

14. Strouse JJ, Jordan LC, Lanzkron S, Casella JF. The excess burden of stroke in hospitalized adults with sickle cell disease. Am J Hematol. 2009;84(9):548–52.
15. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. Lancet Neurol. 2018;17(9): 790–801.
16. Kanter J, Liem RI, Bernaudin F, Bolaños-Meade J, Fitzhugh CD, Hankins JS, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 2021;5(18):3668–89.
17. Hawkins LM, Sinha CB, Ross D, Yee MEM, Quarmyne MO, Krishnamurti L, et al. Patient and family experience with chronic transfusion therapy for sickle cell disease: a qualitative study. BMC Pediatr. 2020;20(1):172.
18. Stegenga KA, Ward-Smith P, Hinds PS, Routhieaux JA, Woods GM. Quality of life among children with sickle cell disease receiving chronic transfusion therapy. J Pediatr Oncol Nurs Off J Assoc Pediatr Oncol Nurses. 2004;21(4): 207–13.
19. Webb J. Social aspects of chronic transfusions: addressing social determinants of health, health literacy, and quality of life. Hematology. 2020;2020(1):175–83.
20. Schlenz AM, Phillips SM, Mueller M, Melvin CL, Adams RJ, Kanter J. Barriers and facilitators to chronic red cell transfusion therapy in pediatric sickle cell anemia. J Pediatr Hematol Nurs. 2022;39(4):209–20.
21. Badawy SM, Beg U, Liem RI, Chaudhury S, Thompson AA. A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy. Blood Adv. 2021;5(2):570–83.
22. Bernaudin F, Verlhac S, Peffault de Latour R, Dalle JH, Brousse V, Petras E, et al. Association of matched sibling donor hematopoietic stem cell transplantation with transcranial doppler velocities in children with sickle cell anemia. JAMA. 2019;321(3):266–76.
23. Hulbert ML, Fields ME, Guilliams KP, Bijlani P, Shenoy S, Fellah S, et al. Normalization of cerebral hemodynamics after hematopoietic stem cell transplant in children with sickle cell disease. Blood. 2023;141(4):335–44.
24. Carpenter JL, Nickel RS, Webb J, Khademian Z, Speller-Brown B, Majumdar S, et al. Low rates of cerebral infarction after hematopoietic stem cell transplantation in patients with sickle cell disease at high risk for stroke. Transplant Cell Ther. 2021;27(12):1018.e1–1018.e9.
25. Al-Jefri A, Siddiqui K, Al-Oraibi A, Al-Seraihy A, Al Ahmari A, Ghemlas I, et al. Hematopoietic stem cell transplantation stabilizes cerebral vasculopathy in high-risk pediatric sickle cell disease patients: evidence from a referral transplant center. J Hematol. 2022;11(1):8–14.
26. Coates TD, Wood JC. How we manage iron overload in sickle cell patients. Br J Haematol. 2017;177(5):703–16.
27. Pack-Mabien A, Brown B, Herbert DE, Haynes J. Iron overload in adults with sickle cell disease who have received intermittent red blood cell transfusions. J Am Assoc Nurse Pract. 2015; 27(10):591–6.
28. Wilson SR, Sears M, Williams E, Drapekin J, Sivakumar I, Padrino S, et al. Gaps in the diagnosis and management of iron overload in sickle cell disease: a "real-world" report from the GRNDaD registry. Br J Haematol. 2021;195(5): e157–60.
29. Stanley HM, Friedman DF, Webb J, Kwiatkowski JL. Transfusional iron overload in a cohort of children with sickle cell disease: impact of magnetic resonance imaging, transfusion method, and chelation. Pediatr Blood Cancer. 2016;63(8): 1414–8.
30. Dolatkhah R, Dastgiri S. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. Cochrane Database Syst Rev. 2020;16(1):CD007843.
31. Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood. 2013;122(6):1062–71.
32. Viayna E, Gehrie EA, Blanchette C, Meny GM, Noumsi G, Huber M, et al. Red cell alloimmunization is associated with increased health care costs, longer hospitalizations, and higher mortality. Blood Adv. 2022;6(20):5655–8.
33. Kacker S, Ness PM, Savage WJ, Frick KD, Shirey RS, King KE, et al. Cost-effectiveness of prospective red blood cell antigen matching to prevent alloimmunization among sickle cell patients. Transfusion (Paris). 2014;54(1):86–97.
34. Gehrie EA, Ness PM, Bloch EM, Kacker S, Tobian AAR. Medical and economic implications of strategies to prevent alloimmunization in sickle cell disease. Transfusion (Paris). 2017;57(9):2267–76.
35. Allen ES, Nelson RC, Flegel WA. How we evaluate red blood cell compatibility and transfusion support for patients with sickle cell disease undergoing hematopoietic progenitor cell transplantation. Transfusion (Paris). 2018;58(11):2483–9.
36. McLaughlin JF, Ballas SK. High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program. Transfusion (Paris). 2016;56(5):1014–21.
37. Greenway A, Ware RE, Thornburg CD. Long-term results using hydroxyurea/phlebotomy for reducing secondary stroke risk in children with sickle cell anemia and iron overload. Am J Hematol. 2011;86(4):357–61.
38. Yu T, Campbell T, Ciuffetelli I, Haywood C Jr, Carroll CP, Resar L, et al. Symptomatic avascular necrosis: an understudied risk factor for acute care utilization by patients with SCD. South Med J. 2016;109(9):519–24.
39. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. Blood. 2012;120(18):3647–56.
40. Adekile A, Menzel S, Gupta R, Al-Sharida S, Farag A, Haider M, et al. Response to hydroxyurea among Kuwaiti patients with sickle cell disease and elevated baseline HbF levels. Am J Hematol. 2015;90(7):E138–9.
41. Adekile AD, Gupta R, Al-Khayat A, Mohammed A, Atyani S, Thomas D. Risk of avascular necrosis of the femoral head in children with sickle cell disease on hydroxyurea: MRI evaluation. Pediatr Blood Cancer. 2019;66(2):e27503.
42. Gupta R, Adekile AD. MRI follow-up and natural history of avascular necrosis of the femoral head in Kuwaiti children with sickle cell disease. J Pediatr Hematol Oncol. 2004;26(6):351–3.
43. Tolu SS, Crouch A, Choi J, Gao Q, Reyes-Gil M, Ogu UO, et al. Hydroxyurea and fetal hemoglobin effect on leg ulcers in patients with sickle cell disease. Ann Hematol. 2022;101(3): 541–8.

44. Lanzkron S, Manwani D, Desai P, Kanter J, Little J. GRNDaD: big data and sickle cell disease. Blood Adv. 2022; 6(3):1088.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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