CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Hydroxyurea as an Alternative to Blood Transfusions for the Prevention of Recurrent Stroke in Children With Sickle Cell Disease

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Children with sickle cell disease (SCD) and stroke receive chronic transfusions to prevent stroke recurrence. Transfusion risks including infection, erythrocyte allosensitization, and iron overload suggest a need for alternative therapies. We previously used hydroxyurea (HU) and phlebotomy in two young adults with SCD and stroke as an alternative to transfusions. We have now prospectively discontinued transfusions in 16 pediatric patients with SCD and stroke. Reasons to discontinue transfusions included erythrocyte alloantibodies or autoantibodies, recurrent stroke on transfusions, iron overload, noncompliance, and deferoxamine allergy. HU was started at 15 mg/kg/d and escalated to 30 mg/kg/d based on hematologic toxicity. Patients with iron overload underwent phlebotomy. The children have been off transfusions 22 months, (range, 3 to 52 months). Their average HU dose is 24.9 ± 4.2 mg/kg/d, hemoglobin concentration is 9.4 ± 1.3 g/dL, and mean corpuscular volume (MCV) is 112 ± 9 fL. Maximum percentage fetal hemoglobin (%HbF) is 20.6% ± 8.0% and percentage HbF-containing erythrocytes (%F cells) is 79.3% ± 14.7%. Fourteen patients underwent phlebotomy with an average of 8,993 mL (267 mL/kg) removed. Serum ferritin has decreased from 2,630 to 424 ng/mL, and 4 children have normal ferritin values. Three patients (19%) had neurological events considered recurrent stroke, each 3 to 4 months after discontinuing transfusions, but before maximal HU effects. These preliminary data suggest some children with SCD and stroke may discontinue chronic transfusions and use HU therapy to prevent stroke recurrence. Phlebotomy is well-tolerated and significantly reduces iron overload. Modifications in HU therapy to raise HbF more rapidly might increase protection against stroke recurrence.

STROKE IS one of the most devastating clinical complications that occurs in children with sickle cell disease (SCD) and is an important cause of death in this patient population.[1-3] Approximately 5% to 10% of children with SCD will develop a stroke, most often in the first decade of life.[4,5] The pathological event is usually infarctive and results from stenosis or occlusion of the large vessels, especially the internal carotid and proximal cerebral arteries.[6,7] Despite prompt aggressive medical intervention, including complete blood exchange, many children with SCD and stroke have residual physical and neuropsychological deficits.[8-10]

Several studies have documented a high rate of stroke recurrence in children with SCD who receive no specific preventive therapy. A report from the Jamaican pediatric cohort described stroke recurrence in 6 of 13 children (46%), with a median interval to recurrence of 9 months after the first stroke.[4] Powars et al[11] reported a recurrence rate of 67% in 15 long-term survivors of stroke, with a temporal clustering of additional neurological events in the first 24 to 36 months after the initial stroke. Russell et al[12] reported stroke recurrence in 9 of 10 (90%) of untransfused pediatric patients with SCD and stroke.

Because of this high risk of stroke recurrence, affected children are typically treated with monthly erythrocyte transfusions designed to reduce the concentration of sickled erythrocytes.[13,14] A chronic transfusion regimen is at least 80% to 90% successful in preventing stroke recurrence,[12,15-18] although the optimal duration of transfusions is not known. A 70% stroke recurrence rate was observed after the prospective discontinuation of a short-term (1- to 2-year) transfusion regimen,[19] and a 50% recurrence rate was observed after prospective discontinuation of a long-term (5- to 12-year) transfusion regimen.[20] Most pediatric hematologists, therefore, recommend indefinite chronic transfusions to prevent recurrent stroke, despite the long-term risks of transfusions, including the possible transmission of infectious agents, erythrocyte allosensitization, and iron overload.

We recently reported two young adults with SCD and stroke who were unable to continue chronic transfusion therapy; transfusions were discontinued, and the patients were treated with oral hydroxyurea (HU) as prophylaxis against stroke recurrence.[21] A phlebotomy program was used to reduce iron overload and stimulate endogenous erythropoiesis. Both patients responded to the HU therapy with elevated levels of fetal hemoglobin (HbF) and HbF-containing erythrocytes (F cells) and had no stroke recurrence during nearly 3 years of HU therapy. In addition, each patient tolerated phlebotomy well and had diminution in serum ferritin values, suggesting a reduction in total body iron stores. Based on this anecdotal success, we prospectively discontinued erythrocyte transfusions in a new and larger cohort of pediatric patients with SCD and stroke. We used daily oral HU therapy to help prevent stroke recurrence and an aggressive periodic phlebotomy regimen to reduce iron overload. Our preliminary results suggest that some children with SCD and stroke may be able to discontinue chronic transfusions and use daily oral HU therapy as stroke prophylaxis. Phlebotomy is well-tolerated and significantly reduces serum ferritin values.

MATERIALS AND METHODS

Patient selection. A total of 25 patients with SCD and stroke who were followed by the Duke University Pediatric Sickle Cell Program (Durham, NC) were considered for this protocol. Sixteen patients were

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Submitted February 16, 1999; accepted June 28, 1999.

Supported in part by the Duke Children's Miracle Network Telethon.

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0006-4971/99/9409-0004$3.00/0

identified who had clinical events or sequelae that suggested they would be unable to tolerate indefinite chronic erythrocyte transfusion therapy. Reasons to consider discontinuing transfusions included erythrocyte alloimmunization, erythrocyte autoantibody formation, recurrent stroke on transfusion therapy, iron overload (serum ferritin >2,000 ng/mL), and noncompliance with transfusion or chelation regimens. The remaining 9 patients were not offered enrollment, because they had received blood transfusions for less than 2 years or had no clinical or laboratory contraindications to continuing chronic transfusion therapy. The study protocol was approved by the Duke University Medical Center Institutional Review Board, and the consent form described the high risk of recurrent stroke once transfusions were stopped. In all cases, at least two different health care providers independently discussed the risks and benefits with each family before enrollment.

Discontinuation of transfusions and initiation of hydroxyurea therapy. Before discontinuing transfusions, patients were screened for abnormal hepatic or renal function, and also for exposure to hepatitis A, B, and C, as well as the human immunodeficiency virus. Approximately 2 weeks after the last transfusion, at a time when endogenous erythropoiesis was recovering, oral HU therapy was started at a dose of 15 mg/kg/d. The dose of HU was escalated by 5 mg/kg/d every 8 weeks as tolerated, up to a maximum of 30 mg/kg/d. If a patient developed hematologic toxicity, defined as a hemoglobin concentration <5.0 g/dL, an absolute neutrophil count of $<1.5 \times 10^9$/L, or a platelet count $<80 \times 10^9$/L, HU therapy was held until blood counts normalized.

Phlebotomy regimen. Patients with laboratory evidence of iron overload were started on a periodic phlebotomy program designed to remove excess iron and stimulate erythropoiesis. Phlebotomy was typically performed in the outpatient setting by the Duke pediatric hematology/oncology nursing staff. Five children also had phlebotomy periodically performed at home by trained pediatric nurses from a home health care agency. Using peripheral access, 5 to 10 mL/kg of venous blood was removed over 20 to 40 minutes and discarded. Vital signs were monitored every 10 minutes. Intravascular volume was replaced using an equivalent volume of normal saline given intravenously over 30 minutes. Phlebotomy was initially performed every 4 weeks, but an interval of 2 weeks was tolerated well by most patients.

Quantitation of HbF and F cells. Measurement of HbF and F cells was performed every 8 weeks. The %HbF was determined using the 2-minute alkali denaturation procedure, and the %F cells using an immunophenotype assay as previously described.[22]

Statistical analysis. All clinical and laboratory data were maintained in a Microsoft Excel database (Redmond, WA). Descriptive statistics were calculated using the Primer of Biostatistics (McGraw-Hill, New York, NY). The Wilcoxon Signed Rank Test (Statview, SAS Institute, Cary, NC) was used to compare serum ferritin values before and after phlebotomy.[23]

RESULTS

Characteristics of the patients. Each of the 16 eligible patients (11 males, 5 females) chose to enroll in this study. Clinical characteristics are summarized in Table 1. Fifteen of the children have a diagnosis of homozygous sickle cell anemia (HbSS), whereas one child has a diagnosis of HbS/O_{Arab}. The mean age (±1 standard deviation [SD]) at first stroke was 7.1 ± 4.4 years, with a median of 6.4 years. In all cases, the initial stroke was infarctive, including 7 presenting with right hemiparesis (4 with concomitant aphasia), 4 with left hemiparesis, 4 with focal neurological deficitis, and 1 with coma and seizures.

Each patient had previously received erythrocyte tranfusions to prevent stroke recurrence, mean duration of 56 ± 36 months, median 51 months (Table 1). Fifteen children had received transfusions for at least 1 year; one (#3) discontinued transfusions after 7 months because of erythrocyte autoantibody and alloantibody formation. All 16 children had received blood via simple erythrocyte transfusions, but 7 also received partial exchange transfusions and 10 had erythrocytapheresis as previously described.[24] One patient (#16) was seropositive to hepatitic C. Nine patients were prescribed deferoxamine (DFO) chelation therapy; 2 were compliant, 5 were noncompliant, and 2 were allergic. Patient #8 developed a generalized pruritic rash with periorbital edema; DFO desensitization was attempted, but was unsuccessful. Patient #12 had significant pain and swelling at the DFO infusion site with a maculopapular rash on the arms and chest; desensitization was not attempted.

Table 1. Clinical Characteristics of 16 Pediatric Patients With SCD and Stroke Who Discontinued Chronic Transfusions and Received Oral Hydroxyurea Therapy to Prevent Stroke Recurrence

Patient No.	Hemoglobin Diagnosis	Age at First Stroke (yr)	Type of Stroke	Transfusions		Reasons to Stop Transfusions	Age Transfusions Stopped (yr)
				mo	Type		
1	SS	12.3	R hemiplegia	82	S, E, P	AlloAb, AutoAb, Iron, NC	19.1
2	SS	4.5	R exotropia	47	S, E, P	AutoAb, NC	8.4
3	SS	5.7	L hemiplegia	7	S	AutoAb	6.3
4	SS	7.7	R hemiplegia, aphasia	13	S	2nd stroke on transfusions	8.8
5	SS	6.5	L hemiplegia	72	S, E, P	AlloAb, AutoAb	16.7
6	SS	6.4	R hemiplegia, aphasia	72	S, E, P	Iron, NC	12.3
7	SS	5.3	R hemiplegia, aphasia	37	S, E	Iron	8.4
8	SS	5.5	Coma, seizures	127	S, E, P	Iron, DFO allergy	16.1
9	SS	6.5	R hemiplegia	79	S, P	Iron, NC	13.1
10	SS	8.3	R hand	34	S, E	Iron, NC	11.2
11	SS	17.3	L hemiplegia	28	S, E	NC	19.7
12	SS	3.0	L hemiplegia	54	S	Iron, DFO allergy	7.6
13	SS	15.0	R hemiplegia, aphasia	39	S, E	Iron, NC	18.4
14	SO_{Arab}	1.1	L hand	22	S	Iron	2.9
15	SS	6.3	R hemiplegia	54	S, E, P	Iron	10.7
16	SS	2.7	L hand	127	S	Iron	13.3

Abbreviations: R, right; L, left; S, simple transfusions; E, erythrocytapheresis; P, partial exchange transfusions; AlloAb, erythrocyte alloantibodies; AutoAb, erythrocyte autoantibodies; DFO, deferoxamine; NC, noncompliance; SS, homozygous sickle cell anemia; SO_{Arab}, heterozygous HbS and HbO_{Arab}.

The reasons to consider discontinuing transfusions varied among the 16 patients (Table 1). Four developed erythrocyte autoantibodies, as recently described.[25] Two of these patients also developed multiple erythrocyte alloantibodies; patient #1 developed alloantibodies to the public Di^b antigen and to a variant D antigen, whereas patient #5 developed alloantibodies to C, Js^a, and Le^a antigens.[25] Additional reasons to consider discontinuing transfusions included recurrent stroke while on transfusions (n = 1), iron overload (n = 11), and noncompliance with the transfusion regimen (n = 4) or chelation therapy (n = 5). At the time that transfusions were stopped, the patients had a mean age of 12.1 ± 4.9 years, median 11.8 years.

Hydroxyurea therapy. The patients have received oral HU therapy for a mean duration of 22 ± 14 months, median 22 months (Table 2). The current average HU dose is 24.9 ± 4.2 mg/kg/d, range 19.1 to 32.7 mg/kg/d. Hematologic toxicity has been mild, with only occasional episodes of transient, reversible myelosuppression (not shown).

Representative data illustrating the hematologic effects of HU therapy are shown in Table 2. Recent laboratory values include a mean hemoglobin concentration of 9.4 ± 1.3 g/dL (median 9.3 g/dL) and a mean corpuscular volume (MCV) of 112 ± 9 fL (median 110 fL). Using the maximal laboratory values for each patient during HU therapy, the mean %HbF is 20.6% ± 8.0% (median 21.7%), whereas the mean %F cells is 79.3% ± 14.7% (median 85.7%).

Phlebotomy regimen. Fourteen of the children had laboratory evidence of iron overload and have received phlebotomy for a mean duration of 18 ± 12 months, median 18 months (Table 2). The total volume of blood removed has ranged from 1,835 to 19,825 mL, with a median volume of 8,993 mL. When calculated in milliliters of blood removed per kilogram of body weight, the phlebotomy volume has ranged from 48 to 405 mL/kg, with a median volume of 267 mL/kg (Table 2).

Serum ferritin values before and after phlebotomy are also shown in Table 2. The 14 children who received phlebotomy had an initial median ferritin value of 2,630 ng/mL, and their most recent median ferritin value has fallen to 424 ng/mL. Seven of the 14 phlebotomized patients currently have a serum ferritin value under 500 ng/mL (Table 2). A comparison of initial and latest serum ferritin values shows a significant diminution in response to phlebotomy, $P = 0.0015$ by Wilcoxon Signed Rank Test.

Clinical events. No patient developed acute chest syndrome or other non-neurological vaso-occlusive events requiring transfusions while on HU therapy. Six children (38%) had minor painful events requiring outpatient analgesia; patients #1 and #6 were hospitalized once for management of pain. Three patients had new neurological events consistent with recurrent stroke. Patient #13 had a severe occipital headache 13 weeks after discontinuing transfusion therapy. Magnetic resonance imaging (MRI) showed a new occipital infarction, and monthly transfusion therapy was restarted. Patient #15 developed right hemiparesis 16 weeks after discontinuing transfusion therapy, and MRI showed a recurrent left cortical infarction. Her symptoms resolved after double-volume exchange transfusion, and she resumed monthly erythrocytapheresis. Patient #16 had isolated left-hand weakness 11 weeks after starting HU therapy; brain MRI was normal, but diffusion studies were consistent with a new left cortical infarct. His symptoms quickly resolved after exchange transfusion, and he also resumed monthly transfusions. No patient has experienced a hemorrhagic neurological event while on HU therapy.

DISCUSSION

Our results provide the first preliminary data to suggest that hydroxyurea may be effective in the clinical setting of cerebrovascular disease in patients with SCD. The 16 pediatric patients with stroke who enrolled in this protocol discontinued transfusions prospectively after receiving blood for an average of almost 5 years, presumably with a substantial (≈50%) risk of stroke recurrence.[20] The reasons to discontinue blood transfusions varied among our patients (Table 1) and included an inability to find compatible blood because of severe erythrocyte

Table 2. Laboratory Parameters for 16 Pediatric Patients With SCD and Stroke Who Discontinued Chronic Transfusions and Began Oral HU Therapy to Prevent Stroke Recurrence

Patient No.	HU Therapy (mo)	HU Dose (mg/kg/d)	Hb (g/dL)	MCV (fL)	HbF (%)	F Cells (%)	Phlebotomy			Ferritin (ng/mL)	
							mo	Total mL	mL/kg	Initial	Latest
1	52	32.7	8.6	102	15.7	69.9	45	19,562	322	8,830	2,962
2	38	19.9	8.6	122	28.1	90.3	35	15,030	405	2,628	419
3	37	26.4	10.3	116	29.6	95.0	ND	ND	ND	560	225
4	36	29.9	10.5	107	31.2	95.8	19	7,412	282	2,153	90
5	33	20.1	10.5	114	27.9	89.0	14	4,460	90	1,025	169
6	27	19.1	10.1	116	20.6	85.0	27	17,090	326	5,950	1,911
7	23	28.1	9.0	100	11.9	58.7	20	8,765	308	2,631	235
8	22	27.0	10.0	129	23.6	88.5	23	19,825	306	4,206	1,326
9	21	27.8	8.0	123	18.3	78.8	21	9,590	261	7,281	3,161
10	20	21.8	8.8	104	27.8	90.0	17	12,695	272	2,877	128
11	16	20.1	11.9	112	22.7	86.3	ND	ND	ND	267	188
12	14	25.3	10.6	122	29.2	95.9	14	9,220	233	2,012	424
13	3	23.8	7.5	107	13.3	69.5	3	3,000	48	2,486	1,309
14	10	30.0	9.5	104	11.2	55.0	10	3,610	194	2,081	319
15	4	22.2	7.4	108	8.2	63.4	4	1,835	58	1,808	1,297
16	3	24.5	8.8	105	9.6	57.5	3	2,450	60	2,700	ND

The %HbF and %F cells refer to the maximal values during HU therapy. The initial ferritin refers to the time that transfusions were discontinued.
Abbreviations: Hb, recent hemoglobin concentration; MCV, recent mean corpuscular volume; ND, not done.

alloimmunization or autoantibody formation,[24] recurrent stroke while on transfusions, noncompliance with the transfusion or chelation regimen, and severe iron overload with DFO allergy. Several of our patients had a very high risk for recurrence, including one child (#4) who had a second stroke while on transfusions and 2 others (#3, #14) who had received transfusions for less than 24 months (Table 1). With a median follow-up of 22 months, our patients had a stroke recurrence rate of only 19%, suggesting that HU therapy may have helped to prevent recurrent stroke. In comparison, the stroke recurrence rate at our institution for patients receiving chronic transfusion therapy is approximately 11%, similar to that recently reported by Pegelow and colleagues.[18]

The mechanisms by which HU might provide protection against stroke recurrence are not known, but the increase in HbF parameters (%HbF and %F cells) likely is important in the prevention of in vivo sickling within the stenotic cerebral vessels. Our patients achieved an average %HbF of approximately 20% and %F cells of approximately 80% (Table 2), values that should inhibit intracellular sickling.[26] Additional possible mechanisms include reductions in total white blood cell count and absolute neutrophil count that accompany HU therapy,[27-29] as well as improved rheological characteristics of the erythrocytes caused by changes in erythrocyte morphology, adhesiveness, and cation content.[30,31]

Each of the recurrent neurological events occurred approximately 3 to 4 months after discontinuing transfusion therapy. This is likely the period of highest risk for stroke recurrence, during which endogenous HbS-containing erythrocytes are replacing the transfused erythrocytes, but before the maximal beneficial hematologic effects of HU therapy. The recently completed pediatric HU safety trial (HUG-KIDS), using the same HU dose escalation schedule, showed that the hemoglobin concentration, MCV, %HbF, and %F cells increase during the first 6 months of HU therapy, but continue to increase between 6 and 12 months of therapy.[29] At the time of their stroke recurrence, our 3 children had an average %HbF level of only 10.4%, well below the %HbF levels achieved by the other patients after prolonged HU therapy. More rapid escalation of the HU dose, or initiating HU therapy several months before discontinuing transfusions, might lead to a more rapid rise in HbF parameters and help prevent these cases of early stroke recurrence. Importantly, no patient experienced a hemorrhagic neurological event as was previously described in a 20-year-old male with cerebrovascular disease receiving HU therapy.[32]

The phlebotomy program was designed to reduce the iron burden and stimulate erythropoiesis, thereby increasing the number of HbF-containing reticulocytes and preventing stroke recurrence. The phlebotomy regimen has been very well tolerated, and most patients have 10 mL/kg blood removed every 2 weeks while maintaining a hemoglobin concentration above 8 g/dL (Table 2). Phlebotomy has led to steady reductions in the total body iron stores, with substantial diminution in the serum ferritin of all 14 patients who received phlebotomy. Seven of the 14 patients who received phlebotomy currently have a serum ferritin <500 ng/mL, and phlebotomy has been discontinued in 4 children whose ferritin values decreased to approximately. 200 ng/mL. These results compare favorably with those reported for patients with beta-thalassemia, who received phlebotomy after curative allogeneic bone marrow transplantation and had eventual mobilization of tissue iron and reduction in liver iron concentration.[33] Although we have not performed a quantitative liver biopsy for iron burden on our patients, one had superconducting susceptometry (SQUID) analysis performed after stopping phlebotomy and was found to have normal hepatic iron stores. SQUID analysis or liver biopsy may be necessary in selected patients to confirm normalization of hepatic iron.

HU has been shown to be effective in reducing the number of painful events, transfusions, and episodes of acute chest syndrome in adults with sickle cell anemia.[34] Similar clinical benefits have been reported in small groups of pediatric patients.[35-39] Based on our encouraging preliminary single-institution results, we believe that larger multicenter trials may be warranted to determine the clinical efficacy of HU in pediatric patients with sickle cell disease, especially in the setting of cerebrovascular disease. To test formally the efficacy of HU in preventing recurrent stroke, children could receive prophylactic erythrocyte transfusions for 2 to 3 years after the initial event, then randomize to either (1) continued transfusions with iron chelation or (2) HU and phlebotomy to alleviate iron overload. The study end points should include not only recurrent clinical neurological events and changes in brain MR imaging and angiography, but also financial costs, quality of life, and the possible sequelae of continued transfusion therapy such as transmission of infection, erythrocyte allosensitization, and iron overload. Improved testing of blood units for infectious pathogens and the use of antigen matching has reduced much of the morbidity associated with chronic erythrocyte transfusion therapy, but iron overload remains a serious long-term problem.[40] Finally, HU could also be considered for the prevention of primary stroke. Adams et al[41] have recently shown that transcranial doppler (TCD) can identify children with SCD who have an increased risk of primary stroke, and that transfusion therapy can prevent primary stroke in this clinical setting.[42] As additional children with SCD and elevated TCD values become identified, perhaps HU therapy should be considered as an alternative to chronic transfusions in this asymptomatic population of patients.

NOTE ADDED IN PROOF

Patient 11, who was originally noncompliant with transfusions, became noncompliant with hydroxyurea after 17 months and refused further therapy. Four months later he developed a recurrent left hemiplegia.

ACKNOWLEDGMENT

The authors thank Dr Thomas R. Kinney and Erin O'Branski for support of this clinical protocol and Dr Gary Brittenham for SQUID analysis. The authors are also grateful to the nurses in the Duke Pediatric Hematology/Oncology out-patient clinic, especially Jayne Cash, Anne Fitzgerald, and Karen Lewis, and to the nurses at Pediatric Services of America; without their dedication, the phlebotomy regimen could not have been successfully completed.

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