Published in final edited form as:
J Pediatr. 2012 February ; 160(2): 281–285.e1. doi:10.1016/j.jpeds.2011.07.050.

Effects of Chronic Transfusions on Abdominal Sonographic Abnormalities in Children with Sickle Cell Anemia

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Abstract

Objective—To assess the effects of chronic erythrocyte transfusions on prevalence of sonographic incidence of organ damage in children with sickle cell anemia (SCA).

Study design—Children (n=148; mean age, 13.0 years) with SCA, receiving chronic transfusions (average, 7 years) underwent abdominal sonography at 25 institutions. After central imaging review, spleen, liver and kidney measurements were compared with published normal values. Potential relations between ultrasound, clinical and laboratory data were explored via Analysis of Variance, Student t-test and Cochran Mantel Haenzel tests of non-zero correlation.

Results—Average spleen length was similar to normal children, but over one-third had spleen volumes > 300mL, 15 had previous splenectomy for splenomegaly and 24 had abnormal splenic echotexture. Two-thirds had hepatobiliary disease; 37 had prior cholecystectomy, 46 had gallstones, 16 had gallbladder sludge. Gallbladder disease correlated with older age ($p = 0.002$), longer liver length ($p < 0.001$), longer duration of transfusions ($p = 0.034$) and higher total

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The authors declare no conflicts of interest.

bilirubin ($p < 0.001$). Liver ($p < 0.001$) and renal lengths ($p \leq 0.005$) were larger than published norms.

Conclusions—In children with SCA, long-term transfusion therapy may not prevent development or progression of abdominal organ dysfunction.

Keywords

sickle cell anemia; iron overload; splenomegaly; gallstones; hepatomegaly; nephromegaly

Overt stroke occurs in 5 to 10% of patients with sickle cell anemia (SCA) by 20 years of age and recurs in over 50% of patients if left untreated [1,2]. Chronic red cell transfusion therapy is effective for reducing the risk of recurrent stroke in children with SCA, but can lead to erythrocyte alloantibody or autoantibody formation and almost always results in iron overload. The “Stroke with Transfusions Changing to Hydroxyurea” (SWiTCH) trial was a multi-institutional, Phase III, randomized trial comparing standard therapy (erythrocyte transfusions with iron chelation) to alternative therapy (hydroxyurea with phlebotomy) for the prevention of secondary stroke and management of iron overload in children with SCA and previous stroke (NCT00122980). Secondary objectives of the study included a comparison of alternative to standard therapy for effects on non-neurological events including renal, hepatobiliary and splenic complications. To assess the degree of pre-existing organ damage to the liver, gallbladder, spleen and kidneys in this high risk group of patients, abdominal sonography was performed before randomization.

We now describe the prevalence of abdominal organ dysfunction in this large cohort of children with SCA. We compare baseline abdominal ultrasound findings in the SWiTCH population with published age-matched normal children and prior reports of children with SCA. The potential relations between ultrasound findings and baseline clinical and laboratory data were also assessed. Together, these data document progressive organ dysfunction despite regular transfusion therapy, findings that may have implications regarding the long-term benefits of chronic transfusions for stroke prophylaxis.

Methods

After local institutional review board approval and in accordance with the Health Information Privacy and Portability Act of 1998, informed parental/guardian consent and patient assent (when applicable) were obtained. Subject eligibility included children between the ages of 5 and 18.9 years with SCA (HbSS, HbSβ° thalassemia or $HbSO_{Arab}$), documented stroke after one year of age, at least 18 months of erythrocyte transfusion therapy since primary stroke, and transfusional iron overload [3]. Pre-randomization, baseline abdominal sonograms were performed at 25 participating institutions using a standard scanning procedure developed for SWiTCH. All imaging was de-identified and submitted as hard-copy film early in the study and later in dicom format on compact discs, and centrally reviewed by one masked pediatric radiologist (MBM) who determined the technical adequacy of images and interpreted all radiological findings.

Imaging included the maximum longitudinal (L), anterior-posterior (AP) and transverse (T) measurements of the spleen and kidneys in the transverse and longitudinal planes. Spleen and renal volumes in milliliters (mL) were calculated using the formula for an ellipsoid model: $[L \times AP \times T] \times 0.523$ [4,5]. Liver length was measured in the right lobe with the longitudinal center of the right kidney in the plane of imaging. Liver parenchyma was assessed for homogeneity and focal abnormalities. The presence of gallstones, gallbladder sludge, gallbladder wall thickening (>3 mm), and common bile duct (CBD) dilatation (> 4 mm) were recorded [6]. The spleen was also assessed for parenchymal homogeneity and

focal abnormalities. Kidneys were considered abnormally echogenic if the renal cortex was equal to or more echogenic than adjacent spleen or liver. Renal corticomedullary differentiation was considered abnormal when the cortex was difficult to visually distinguish from medulla [7]. Kidneys were also assessed for the presence of renal calculi, cysts or other focal parenchymal abnormalities.

Liver and gallbladder function were assessed with pre-treatment laboratory studies including serum alanine aminotransferase (ALT), aspartate transaminase (AST), and bilirubin (total and direct) that were centrally analyzed, typically within one week of the ultrasound exam. Normal laboratory thresholds for this laboratory included ALT < 65 U/L, AST < 37 U/mL, total bilirubin < 1.0 mg/dL, and direct bilirubin < 0.3 mg/dL. Renal function was assessed by the blood urea nitrate (BUN) and serum creatinine levels; normal values for these variables increase with increasing patient age.

Clinical assessments included demographics, weight, height, age at index stroke, palpated liver size estimate, history of liver disease, history and indication for prior cholecystectomy or splenectomy, history of hypertension, length of time on red cell transfusion therapy, type of transfusion (erythrocytapheresis, partial exchange or simple), presence of alloantibodies and autoantibodies, results of baseline liver biopsy for quantitation of liver iron content (LIC), and local complete blood counts obtained within 1–2 weeks of baseline ultrasound.

Statistical analysis

The Students t-test or Analysis of Variance (ANOVA) was used to compare baseline laboratory assessments and other continuous measurements between categorical spleen, renal, and liver function groups. When warranted, laboratory measurements such as ALT and AST were log transformed. Spleen, renal, and liver assessments measured on a continuous scale were correlated with other continuous measures using Spearman's rank coefficient. Differences between categorical measures were assessed via Cochran Mantel Haenzel (CMH) tests of non-zero correlation. The student's t-test was performed to compare spleen lengths, renal lengths, and liver lengths of subjects enrolled in the SWiTCH trial with published age-matched hematologically normal children. Cluster analysis was also performed to determine if individual subjects had more than one abnormality. The SWiTCH primary hypothesis was adjusted for multiple comparisons (recurrent stroke rate and change in log LIC). All other p-values should be viewed as descriptive or exploratory analyses. There was no hypothesis testing on a priori hypotheses in this study. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Subjects (n=149) underwent ultrasound imaging at 25 clinical sites; one subject's ultrasound was non-diagnostic for all organs. A small number of sonograms were technically inadequate for assessment of some individual organs, resulting in a slightly variable number of measurements for different abdominal organs. Of the 148 with adequate imaging, the mean age was 13.0 years (range 5–19 years, median 13.3 years), 77 were boys, 147 had HbSS sickle cell disease, and 1 had Hb S-β° thalassemia. The average length of time on transfusion therapy was 7.0 ± 3.7 years (range 1.8 – 15.5 years; median 6.6 years).

For 2 subjects the sonograms were of non-diagnostic quality for spleen assessment. In the remaining 146 subjects the spleen was sonographically visible in 115 and not visible in 31 (31/146, 21%). Children with visible spleens had average splenic volumes of 283.7 mL ± 200.7 mL; many had large spleens including 29 (29/115, 25%) with spleen volumes between 300 and 500 mL and another 15 (15/115, 13%) with volumes > 500 mL. Larger spleen volume was significantly correlated with a lower platelet count ($r = -0.319$, $p = 0.001$).

There was no association between sonographically non-visible spleen and age at index stroke ($p = 0.931$). Subjects with non-visible spleens had significantly higher mean ALT levels (78 ± 64 IU/L vs. 51 ± 28 IU/L; $p = 0.004$) and significantly higher LIC values (mean = 19.4 ± 10.9 mg Fe/g liver dry weight vs. 14.2 ± 8.6 mg Fe/g liver dry weight; $p = 0.021$) than those with visible spleens. Subjects with a history of splenic sequestration and sonographically visible spleens had significantly smaller spleen volumes (n = 11, mean volume = 139.1 ± 94.3 mL) than those without history of sequestration (n = 103, mean volume = 299.2 ± 203.2 mL; $p < 0.001$).

Sonographic spleen length was strongly correlated with spleen volume (r = 0.945, $p < 0.001$). There was no significant difference in the average sonographic spleen lengths of subjects enrolled in the SWiTCH trial compared with age-matched hematologically normal children (Table I). Abnormal splenic echotexture was observed in 24 of 115 (24/115, 21%) visible spleens including inhomogenous splenic echotexture (n = 15), coarse echotexture (n = 3), echogenic echotexture (n = 3), round hypoechoic splenic foci (n = 2) and a round hyperechoic focus (n = 1). Subjects with inhomogenous spleens had a longer duration of transfusion therapy (mean duration 8.2 ± 3.3 yrs vs. 6.3 ± 3.6 yrs; $p = 0.056$) and higher prevalence of alloantibodies (50% vs. 24%, $p = 0.039$) than those with homogenous spleens. There was also a significant association between inhomogenous spleens and older age at enrollment (mean age, 14.6 ± 3.2 years vs. 12.1 ± 4.0 years; $p = 0.023$) and higher LIC (mean LIC 18.6 ± 8.1 mg Fe/g liver dry weight vs. 13.6 ± 8.6 mg Fe/g liver dry weight; $p = 0.024$). There was no relationship between spleen inhomogeneity and age at index stroke ($p = 0.229$). There was no clustering of abnormal spleen findings with other organ abnormalities, and no correlations were identified with either LIC or transfusion duration.

Twenty-three subjects had documented prior surgical splenectomy; three of these subjects had sonographically visible spleens that were felt to represent re-growth of accessory spleens, and two had sonograms that were inadequate for spleen assessment. Therefore, of the 31 subjects with non-visible spleens, 19 (19/31, 61%) had undergone splenectomy and 12 (12/31, 39%) had no reported history of splenectomy, so were considered to have splenic autoinfarction. Seventeen of the 23 surgical splenectomies occurred while subjects were receiving chronic transfusions and were performed for the following indications: splenomegaly and hypersplenism (n = 15), autoimmune hemolytic anemia (n = 1), and unknown (n = 1). Five splenectomies occurred prior to transfusion therapy, all for splenic sequestration, but the timing of one splenectomy was unknown.

A total of 148 subjects had adequate renal imaging. There was a strong correlation between renal lengths and volumes (right kidney, r = 0.85, $p < 0.001$; left kidney, r = 0.84, $p < 0.001$). As expected, greater patient age, height and weight were correlated with increased renal volume (age; r = 0.72, $p < 0.001$: height; r = 0.75, $p < 0.001$: weight; r = 0.75, $p < 0.001$). Renal lengths of subjects enrolled in the SWiTCH trial were significantly larger than age matched published normal values (Table II). There was no significant association between history of hypertension (n = 8) and renal volume ($p = 0.30$). Four subjects had echogenic kidneys, 3 had loss of renal corticomedullary differentiation and one had a simple renal cyst. There was no clustering of abnormal kidney findings with other organ abnormalities, and no correlations were identified with either LIC or transfusion duration.

Similarly, 148 subjects had adequate biliary imaging and 99 (99/148, 67%) had abnormal findings consistent with gallbladder disease: 37 (37/148, 25%) had undergone prior cholecystectomy, and 46 of the remaining 111 (46/111, 41%) had gallstones and another 16 (16/111, 14%) had gallbladder sludge. Additional abnormal biliary findings included common bile duct (CBD) dilatation in 8 (8/111; 7%) and gallbladder wall thickening in 3 (3/111; 3%). The presence of gallbladder disease (prior cholecystectomy, current gallstones

or sludge) was significantly associated with older age at enrollment (mean 13.8 ± 3.7 years vs. 11.8 ± 4.0 years; $p = 0.002$), greater liver length measured on ultrasound (mean 159 ± 21 vs. 142 ± 21 mm; $p < 0.001$), longer duration of transfusion therapy (mean 7.6 ± 3.6 years vs. 6.3 ± 3.8 years; $p = 0.034$) and higher total serum bilirubin (mean 3.8 ± 2.5 mg/dL vs. 2.5 ± 1.1 mg/dL; $p < 0.001$). Gallbladder disease was not associated with serum ALT, AST, erythrocyte alloantibodies or autoantibodies, type of transfusion (erythrocytapheresis, partial exchange or simple), palpable hepatomegaly, or history of liver disease (all $p \geq 0.070$). Subjects enrolled in the SWiTCH trial had significantly larger, sonographically measured liver lengths than published values for age-matched normal children (Table III).

Discussion

We prospectively assessed the abdominal sonographic sequelae of long-term transfusion therapy in a large cohort of children with SCA receiving regular transfusions for the prevention of secondary stroke. Perhaps the most striking observation was the sonographic evidence of substantial organ dysfunction despite long-term transfusion therapy. In the spleen, for example, over one-third of the subjects had spleen volumes over 300 mL and 15 additional subjects had a history of splenectomy performed for splenomegaly while on transfusions. Children with larger spleens had laboratory evidence of hypersplenism with lower platelet counts. Further, 21% of visible spleens had abnormal echotexture reflecting parenchymal damage, presumably due to a combination of sinusoidal congestion, fibrosis, infarction and possibly iron deposition [8].

Eleven subjects with sonographically visible spleens and history of splenic sequestration had significantly smaller spleens than others and an additional 12 subjects had non-visible spleens due to autoinfarction. Almost 80% of spleens were sonographically visible with average length equivalent to age-matched normal controls (Table I), suggesting some preservation of splenic tissue [8]. Our findings agree with previous investigators who have reported an incidence of “splenomegaly” from 14% to 32% and abnormally “small spleens” ranging from 6% to 33% in children and adults with HbSS disease [9,10]. Unfortunately, those reports did not provide sonographic measurements of solid organ sizes (spleen, liver or kidneys), so we cannot directly compare measurements obtained from our cohort to them. Further, prior reports do not specify whether subjects were receiving transfusion therapy for SCA when ultrasound data were obtained. Our findings indicate that the spleen is not necessarily well preserved despite years of regular chronic transfusion therapy, and splenomegaly with hypersplenism and autoinfarction are common findings. It is noteworthy that we found a very strong correlation between sonographic spleen length and volume. Therefore, sonographic measurement of spleen length alone or palpation may be sufficient to assess spleen size and volume in this patient population.

In our study splenectomized subjects had significantly higher ALT and LIC levels than those with sonographically visible spleens. Although these subjects also had longer duration of transfusion therapy likely leading to increased liver iron deposition and subsequent liver dysfunction, it is possible that the spleen acts as a reservoir for iron deposition that protects the liver from iron overload and organ damage. This hypothesis is supported by the findings of Brewer et al who found that in chronically transfused patients with SCA, splenic iron concentration measured by magnetic resonance R2 and R2* continued to increase with increasing LIC [11]. These investigators also found that splenectomized subjects showed a trend toward higher LIC compared with subjects with spleens. Further prospective studies are needed to determine the relationship between splenic and liver iron deposition in patients with SCA receiving chronic red blood cell transfusions.

Nephromegaly is known to occur in children and adults with sickle cell disease and has been shown to correlate with glomerular hyperfiltration [9,10,12]. The etiology of renal enlargement is not known but is postulated to be due to glomerular hypertrophy and increased renal blood volume, perhaps related to chronic anemia and repeated parenchymal sickling [13]. Chronic transfusion therapy does not appear to protect the kidneys from these effects because renal lengths of subjects enrolled in the SWiTCH trial were significantly larger than age-matched hematologically normal children (Table II).

Hepatobiliary disease was also a common finding among subjects enrolled in the SWiTCH trial with a high prevalence of prior cholecystectomy (37/148; 26%), as well as current gallstones (46/111; 41%) or gallbladder sludge (16/111;14%). These findings are at least comparable with prior reports for children and adults with HbSS disease [9,10]. Although others have shown that transfusions may decrease the rate of hemolysis in children with SCA, it is possible that chronic transfusions with alloantibody formation may increase hemolysis and accelerate the formation of sludge and cholelithiasis [14]. We found that the presence of gallbladder disease was associated with older age at study entry, length of transfusion therapy, sonographically measured liver length and serum total bilirubin concentration. Also consistent with prior reports, our sonographically measured liver lengths were significantly longer than age matched, hematologically normal children. Therefore, chronic transfusion therapy does not appear to protect the known hepatobiliary sequelae of SCA, and could even increase the development of cholelithiasis.

An important limitation of our study is that the underlying prevalence of organ dysfunction and abdominal ultrasound abnormalities prior to initiation of transfusion therapy in our cohort is unknown. Although a retrospective review of abdominal sonography performed on these same children, or another cohort of non-transfused children with SCA, may have provided useful information, this imaging was not available for comparison. However, given the high incidence of spleen, renal, and hepatobiliary disease among subjects enrolled in the SWiTCH trial, despite an average of 7 years of transfusion therapy, our data demonstrate that chronic transfusion therapy is insufficient to reverse or prevent organ damage and dysfunction in children with SCA. These findings are concordant with those of Hulbert et al who recently reported progressive cerebrovascular disease and evidence of ongoing cerebral infarction and vasculopathy in a cohort of 40 children with SCA receiving chronic transfusions for secondary stroke prevention [15]. Another potential limitation is the possibility that iron overload from chronic transfusions also contributed to the observed organ dysfunction. However, the lack of correlation between LIC or transfusion duration and organ abnormalities argues against this possibility.

In this large SWiTCH cohort, subjects were receiving regular transfusions designed to keep the HbS concentration < 30% of the total hemoglobin concentration, yet presumably erythrocytes capable of sickling within the microcirculation still cause progressive abdominal organ parenchymal damage. Pre-enrollment %HbS values averaged 35% for the SWiTCH cohort [16] but were 30% at the time subjects joined the study. These findings have implications for the potential long-term benefits of chronic transfusion therapy in children with SCA, suggesting that abdominal organ dysfunction continues despite regular transfusions. Future analyses of SWiTCH treatment results will help compare the effects of hydroxyurea versus transfusions on organ damage in this high-risk patient population.

Acknowledgments

Supported by the National Heart, Lung and Blood Institute (grants U01-HL078787 and U01-HL078987).

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Table I

Comparison of spleen lengths of subjects enrolled in the SWiTCH trial and published age-matched hematologically normal children [4]

	SWiTCH Cohort Spleen Lengths (mm)		Normal Spleen Lengths (mm)		
Age (years)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	***p*-value**
5–6	14	82.5 (20.6)	30	84 (9.0)	0.398
7–8	13	81.5 (23.6)	36	85 (10.5)	0.302
9–10	14	88.1 (22.4)	29	86 (10.7)	0.372
11–12	21	90.0 (23.2)	17	97 (9.7)	0.109
13–14	17	91.5 (30.7)	21	101 (11.7)	0.117
15–16	15	91.4 (24.3)	12	101 (10.3)	0.090
17+	20	74.7 (26.6)	.	.	.

Table II

Comparison of renal lengths of subjects enrolled in the SWiTCH trial and published age-matched hematologically normal children [5]

	SWiTCH Cohort Renal Lengths (mm)			Published Normal Renal lengths (mm)			
Age (years)	**Kidney**	**N**	**Mean (SD)**	**Kidney**	**N**	**Mean (SD)**	***p*-value**
5–6	Right	14	86.9 (8.6)	Right	26	74 (5.5)	<0.001
	Left	14	86.8 (9.8)	Left	26	79 (5.9)	0.005
7–8	Right	15	88.6 (8.6)	Right	32	80 (6.6)	<0.001
	*Left	14	87.1 (7.4)	Left	32	84 (6.6)	0.089
9–10	Right	18	93.1 (6.4)	Right	27	80 (7.0)	<0.001
	*Left	16	93.1 (4.8)	Left	27	84 (7.4)	<0.001
11–12	Right	24	98.2 (10.8)	Right	15	89 (6.2)	<0.001
	Left	24	99.8 (11.5)	Left	15	91 (8.4)	0.005
13–14	Right	20	106.6 (9.7)	Right	22	94 (5.9)	<0.001
	Left	20	106.8 (10.3)	Left	22	96 (8.9)	<0.001
15–16	Right	26	111.7 (11.6)	Right	11	92 (7.0)	<0.001
	Left	26	111.6 (11.8)	Left	11	99 (7.5)	<0.001
17+	Right	31	114.6 (10.0)	Right		.	.
	Left	31	112.2 (10.7)	Left		.	.

*Inadequate imaging of left kidney resulted in different number of right and left kidney measurements

Table III

Comparison of liver length of subjects enrolled in the SWiTCH trial and published values for hematologically normal children [4]

	SWiTCH Cohort Liver Lengths (mm)		Published Normal Liver Lengths (mm)		
Age (years)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	***p*-value**
5 – 6	13	129.1 (18.9)	30	100 (13.6)	<0.001
7 – 8	15	128.8 (10.8)	38	105 (10.6)	<0.001
9 – 10	18	134.4 (12.5)	30	105 (12.5)	<0.001
11 – 12	21	155.0 (20.0)	16	115 (14.0)	<0.001
13 – 14	19	163.2 (15.7)	23	118 (14.6)	<0.001
15 – 16	23	165.2 (15.1)	12	121 (11.7)	<0.001
17+	30	165.1 (19.5)	.	.	