Transfusional Iron Overload in a Cohort of Children with Sickle Cell Disease: Impact of Magnetic Resonance Imaging, Transfusion Method, and Chelation

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**Background.** Transfusions prevent a number of complications of sickle cell disease (SCD), but cause inevitable iron loading. With magnetic resonance imaging (MRI), liver iron can be monitored non-invasively. Erythrocytapheresis can limit iron loading and oral chelation provides a more tolerable alternative to subcutaneous administration. The impact of these factors on control of iron burden in SCD has not been well studied. Procedure. Iron monitoring practices, chelation use, and transfusion methods were assessed in our cohort of pediatric patients with SCD receiving chronic transfusion. The impact of these factors on iron burden was assessed. Results. Among 84 subjects, the proportion that underwent appropriate liver iron concentration (LIC) assessment rose from 21% before to 81% after implementation of R2-MRI in 2006. Among subjects with at least two R2-MRI examinations, median LIC improved (13.2–7.9 mg/g dw, P = 0.027) from initial to final study. Most (67.9%) subjects initially received simple transfusions and subsequently transitioned to erythrocytapheresis. After switching, LIC improved from 13.1 to 4.3 mg/g dw (P < 0.001) after a median of 2.7 years and ferritin improved (2,471–392 ng/ml, P < 0.001) after a median of 4.2 years. Final serum ferritin and LIC correlated negatively with the proportion of transfusions administered by erythrocytapheresis and chelation adherence. Conclusions. Routine liver R2-MRI should be performed in individuals with SCD who receive chronic red cell transfusions. Adherence with chelation should be assessed regularly and erythrocytapheresis utilized when feasible to minimize iron loading or reduce iron stores accumulated during periods of simple transfusion. Pediatr Blood Cancer 2016;63:1414–1418. © 2016 The Authors. Pediatric Blood & Cancer published by Wiley Periodicals, Inc.

**Key words:** magnetic resonance imaging; sickle cell disease; transfusional iron overload

**INTRODUCTION**

Regular red cell transfusion therapy increasingly is being used in the management of children with sickle cell disease (SCD).[1,2] While this treatment effectively reduces the risk of stroke and other complications,[2,3] it is accompanied by iron loading, which may lead to other clinical consequences.

Recent advances in the monitoring and treatment of iron overload appear to have had a positive impact on iron burden, morbidity, and mortality in chronically transfused patients with thalassemia. Liver R2 magnetic resonance imaging (MRI) has almost completely replaced invasive biopsy for the assessment of liver iron in patients with thalassemia in the United States, and in parallel, liver iron concentration (LIC) has significantly improved in this patient population over the past decade.[4] Cardiac T2* MRI, which enables accurate prediction of the risk of developing iron-related cardiac disease,[5] is increasingly utilized to tailor iron chelation treatment in patients with thalassemia,[6] and is a factor contributing to improved survival in this patient population.[7,8] Finally, the availability of oral treatment options, including deferiprox and deferiprone, may improve adherence and control of iron burden compared to subcutaneous infusion with deferoxamine.

The pathophysiology and clinical consequences of transfusional iron overload differ between individuals with SCD and thalassemia. Cardiac iron loading, iron-related cardiomyopathy, and endocrinopathies are less common in SCD than in thalassemia.[9–11] In addition, treatment approach may vary between these two patient populations. Exchange transfusion can be employed to limit iron loading in patients with SCD,[12] but is not generally utilized in thalassemia, while in the United States deferiprone is only labeled for use in individuals with transfusion-dependent thalassemia. Historically, monitoring of iron overload and associated organ injury has been reported to be less optimal in patients with SCD compared to those with thalassemia with similar degrees of transfusional iron loading.[13] Given these important differences, we sought to evaluate the utilization and impact of liver R2-MRI, transfusion method (simple or automated exchange), and chelation on iron burden in children and young adults with SCD followed at our center. We hypothesized that the assessment of LIC and use of oral chelation would increase during the study period, and that LIC and ferritin would improve after R2-MRI was introduced at our center and deferasirox became clinically available (both in early 2006). We also hypothesized that adherence to chelation therapy and use of erythrocytapheresis would be associated with better control of transfusional iron overload.

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Abbreviations: CVL, central venous line; IQR, interquartile range; LIC, liver iron concentration; MRI, magnetic resonance imaging; SCD, sickle cell disease

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METHODS

Subjects

The Institutional Review Board at the Children’s Hospital of Philadelphia approved the study. Informed consent and, where appropriate, child assent were obtained from all participants. Subjects were recruited during routine clinic or transfusion visits between August, 2006 and April, 2013. The design of the study was a prospective longitudinal observational cohort with a component of retrospective data collection that included data from the start of chronic transfusion therapy for each patient. Patients who were receiving regular red cell transfusions for any underlying hematological disorder were eligible for participation, but the current report is limited to subjects with a diagnosis of SCD. For the current analyses, data collected through June 2013 or the date of the final visit to our clinic, if earlier, were utilized.

Data Collection

Data were abstracted from the electronic medical record (Epic Systems Corporation, Verona, WI), apheresis unit records, and paper outpatient clinic charts. Baseline demographic information included SCD diagnosis, indication(s) for chronic transfusion, sex, and age at initiation of transfusion. Assessments of degree of iron overload included serum ferritin level, LIC obtained by spin density projection assisted R2-MRI (FerriScan, Resonance Health, Australia) using standard methodology[14] and/or liver biopsy, and cardiac T2* MRI[15] with data analysis utilizing CMRTools software (Cardiovascular Imaging Solutions, Ltd., London, UK). Liver R2 and cardiac T2* MRI were first utilized for patients with SCD at our Center in 2006. Prior to then, liver biopsy generally was reserved for patients with concerning ferritin levels, abnormal liver function tests, or concomitant hepatitis C infection, or for patients undergoing an intraabdominal surgical procedure, such as cholecystectomy, due to provider and patient concerns about the risks of anesthesia and surgery in patients with SCD. Once R2-MRI became available, LIC assessment was recommended annually. To determine the proportion of subjects who underwent appropriate LIC screening, LIC assessment was defined as indicated if the child had received 2 or more years of transfusion and had a serum ferritin level of 1,000 ng/ml or higher. LIC was categorized as <7 mg/g dw (target range), 7 to <15 mg/g dw (elevated), and ≥15 mg/g dw (very elevated with increased risk of iron-related complications).[16] Chronic transfusion history was collected, including type(s) (simple, erythrocytapheresis) and duration. Abstracted chelation information included chelator agent(s), dose(s), dose adjustments, reasons for dose changes, and adverse effects. Adherence data for each therapy was assessed by chart review of patient report to provider, generally documented as doses per week received. Adherence data were then categorized as good (at least 75% of prescribed doses received) or poor (less than 75% of prescribed doses received).

To determine whether liver R2-MRI results affected clinical management, providing team clinical notes were reviewed for changes in chelation or transfusion that occurred within 3 months of the MRI but were not specifically documented in the clinic note.

Statistical Analysis

Descriptive analyses including mean, standard deviation, median, range, and proportions were used to describe patient characteristics. In exploratory analyses, continuous variables were compared between groups using t-tests or Mann–Whitney U tests. The independence of categorical variables was assessed using chi-square or Fisher exact tests. Relation of LIC to serum ferritin was estimated by Pearson correlation coefficient. Linear regression was employed for multivariate analyses and included all variables with a significance level of 0.1 or less in univariate analysis. All statistical analyses were performed with Stata.

### TABLE I. Patient Characteristics (N = 84)

| Characteristic                     | Initial      | Final        |
|-----------------------------------|--------------|--------------|
| Age, mean (SD), years             | 7.3 (4.1)    | 15.9 (4.8)   |
| Sex, n (%)                        | Male 54 (64.3) | Female 30 (35.7) |
| Genotype, n (%)                   | SS 81 (96.4)  | SC 1 (1.2)    |
| Indication for transfusion, n (%) | Abnormal TCD 36 (42.9) | Recurrent stroke 20 (23.8) |
| No chelation                      | 33 (39.2)    | 50 (59.5)    |
| Chelation, n (%)                  | DFO 11 (13.1) | DFX 22.2 (5.7) |
| Chelation dosing, mg/kg/day, mean (SD) | DFO 35.0 (9.1) | DFX 36.4 (11.4) |
| Iron assessment                   | LIC, mg/g dw, median (range), N = 40 (1.3–41.4) | Ferritin, ng/mL, median (range), N = 84 (11.7–7140) |
| Cardiac T2*, msec, mean (SD), N = 20 | 35.2 (6.8)   | 36.6 (5.8)   |

TCD, transcranial Doppler; MRA, magnetic resonance angiogram; DFO, deferoxamine; DFX, deferasirox; LIC, liver iron concentration; dw, dry weight.
Eighty-four subjects with SCD were enrolled in the study (Table I). These subjects were transfused for a mean duration of 8.6 (median 8.8, range 1.8–19.4) years. The most common indications for transfusion were primary or secondary stroke prevention. Prior to 2006, only seven of 34 children (20.6%) who met criteria for LIC assessment (transfusions for at least 2 years with ferritin >1,000 ng/ml) had LIC performed, all by biopsy. In contrast, by the end of the study, 56 of 69 (81.2%) indicated subjects underwent at least one LIC assessment by R2-MRI.

A total of 146 R2-MRI studies was obtained in 56 children between January, 2006 and June, 2013 (range 1–7 per subject). The median time between R2-MRI studies was 1.3 years (range 0.2–3.7 years). Ninety-five of the 146 liver R2-MRI studies were obtained within 30 days of a serum ferritin test. The correlation coefficient of LIC acquired by R2-MRI with ferritin was 0.733 (\(P < 0.001\)) in this group, and 0.674 (\(P < 0.001\)) when only the first MRI-ferritin pairing was utilized per child. The distribution of LIC values based on serum ferritin obtained within 30 days is shown in Figure 1.

Clinical Decision Making

The results of the liver R2-MRI were specifically documented in the clinic note for 77 (53%) of the MRI studies. The rate of documentation improved from 25% in the first year it was available at our Center to 76.5% in last full year of the study period (\(P = 0.014\)). After specific documentation of R2-MRI result, the next LIC obtained by R2-MRI improved 62.2% of the time compared with 42.2% of the time in those without such documentation (\(P = 0.058\)). Fifteen additional adjustments to treatment were made within 3 months of the MRI without specific clinician documentation. Clinical decisions based on the R2-MRI results are shown in Figure 2. In addition, one subject proceeded to hematopoietic stem cell transplantation following a satisfactory LIC by R2-MRI, and another was determined eligible to enter a clinical trial.

Change in Iron Burden

Forty subjects underwent at least two R2-MRI studies. The median LIC significantly improved from 13.2 (Interquartile range [IQR] 8.2–24) at initial MRI to 7.9 (IQR 3.1–21.1) mg/g dw, \(P = 0.027\) at final MRI, obtained a median of 3.5 (IQR 2.08–5.02) years later. The median ferritin values obtained nearest to these liver MRI studies improved significantly from 2,728 (IQR 1,829–3,732) to 1,363 (IQR 709–4,017) ng/ml, \(P = 0.004\). The distribution of liver iron risk categories improved as well (Fig. 3). Cardiac T2* value was normal (>20 msec) at baseline and follow-up among 20 subjects tested.

Among the entire cohort of 84, the median initial ferritin was 348 (IQR 126–1,244) ng/ml and there was no significant change over the course of the study, with a final ferritin of 475 (IQR 176–2,360) ng/ml, \(P = 0.16\). Both the final ferritin \((R = −0.6048, P < 0.001)\) and final LIC \((R = −0.4118, P = 0.01)\) negatively correlated with the proportion of transfusions received by erythrocytapheresis. The final serum ferritin (1,453 vs. 2,698 ng/ml,
TABLE II. Change in Iron Burden by Transfusion Type

| Variable | Simple only (N = 11) | Erythrocytapheresis only (N = 12) | Erythrocytapheresis after simple (N = 57)* |
|----------|----------------------|----------------------------------|-------------------------------------------|
| Time (y)* | 8.2 (4.9–9.4)        | 3.5 (2–12.2)                     | 4.2 (2–6.4) |
| Initial ferritin (ng/ml) | 373 (150–771) | 120.5 (47.5–186.5) | 2,471 (1,240–5,460) |
| Final ferritin (ng/ml) | 2,620 (1,240–5,460) | 135 (71–188) | 392 (205–1,480) |
| P value | 0.005                | 0.67                             | <0.001                                    |
| Initial LIC (mg/g dw) | 11.7 (6.3–19.7) | –c | 13.1 (9.2–25.2) |
| Final LIC (mg/g dw) | 10.5 (7.9–24.1) | –c | 4.3 (2.1–14.3)d |
| P value | 0.31                 | <0.001                           |                                              |

*Initial values are values at the start of erythrocytapheresis, after a median of 3.7 years of simple transfusion (range 1.1–5.5); btime receiving the transfusion type; cno subjects on erythrocytapheresis alone underwent more than one LIC assessment; dfinal LIC (N = 24) assessed after a median of 2.7 years of erythrocytapheresis (range 2.0–6.4). LIC, liver iron concentration; dw, dry weight.

P = 0.025) and LIC (8.6 vs. 20.7 mg/g dw, P = 0.003) were significantly lower in children whose adherence with chelation was estimated to be at least 75% (regardless of chelator), compared with those who were less adherent. These factors remained significant in multivariate analysis.

Transfusion

Of the 84 subjects, 11 (13.1%) received only simple transfusions, while 12 (14.3%) were managed with erythrocytapheresis alone. Sixty-one (72.6%) received a combination of simple and exchange transfusion, with 57 (67.9%) initially receiving simple transfusions and then transitioning to erythrocytapheresis after a median of 3.7 (IQR 1.9–5.5) years. Overall, the median age at initiation of erythrocytapheresis was 9.9 (IQR 7.9–12.7) years. The change in iron burden by method of transfusion received is shown in Table II.

Eighteen subjects underwent placement of a central venous line (CVL) to receive transfusion therapy. Five CVLs were placed to administer simple transfusions and 15 for erythrocytapheresis (two subjects had a CVL for both transfusion types). Three subjects had the line removed when peripheral access became adequate. Four subjects experienced CVL-associated infections, including one subject who had two separate infections. Nine children (12.5%) while on simple transfusion and 25 (34.2%) on erythrocytapheresis developed new red cell alloimmunization; an additional nine (14.8%) developed new red cell alloantibodies on both types of transfusion.

Chelation

Of 84 subjects, 51 (60.7%) received chelation therapy. The types and mean doses of chelators used at initiation of chelation and at the end of the study are shown in Table I. Overall, 20 subjects ever received deferoxamine and 49 received deferasirox. Of 42 subjects who initiated chelation after deferasirox became commercially available in 2006, 40 began with deferasirox. Thirteen subjects in the study switched from deferasirox to deferoxamine, two due to persistent elevation in hepatic transaminases, and 11 due to iron levels that were worsening or not improving, generally in association with poor adherence to treatment. Four of these children subsequently switched back to deferasirox.

Among 12 subjects who only received erythrocytapheresis, none required chelation therapy. Among 11 subjects who only received simple transfusion, 10 required chelation therapy while the remaining subject had received transfusion for 1.8 years and had not started chelation. Thirty-seven (64.9%) of 57 subjects who began with simple transfusion and transitioned to erythrocytapheresis received chelation while undergoing erythrocytapheresis; these subjects had significantly higher ferritin levels (1,970 vs. 327 ng/ml, P < 0.001) and longer prior duration of simple transfusions [4.6 (IQR 3.7–6.6) vs 2.0 (IQR 1.1–3.4) years, P < 0.001] at the start of erythrocytapheresis compared with children who did not receive chelation. Fourteen subjects (27.5%) discontinued chelation therapy due to normalization of iron stores during the course of the study, all while receiving erythrocytapheresis.

During the study period, eight subjects (16.3%) reported gastrointestinal effects including abdominal pain, emesis, and diarrhea with deferasirox and 10 (20.4%) reported the taste/texture of the deferasirox dispersible tablet as a factor that impeded adherence. Five subjects (10.2%) had elevated hepatic transaminases (more than four times the upper limit of normal). One subject (2.0%) had elevated creatinine with deferasirox, which reversed with temporary chelation hold and did not recur with reinstatement at the prior dose. Four subjects (20%) taking deferoxamine reported skin irritation at the injection site. Average adherence to deferasirox and deferoxamine did not differ significantly.

DISCUSSION

In this cohort of children with SCD receiving regular transfusion therapy, the proportion who underwent appropriate liver iron assessment significantly increased from 21 to 81% after R2-MRI became available. Liver biopsy is invasive, with procedure-related and anesthesia risks that are compounded by the risk of sickle-related complications.[17,18] Patient and provider concerns about these risks contributed to low utilization rates at our center. Indeed, disparately low rates of assessment of LIC in patients with SCD compared with thalassemia have been described.[13] The substitution of ferritin levels for substernal iron burden in this patient population may lead to suboptimal iron management. MRI is a noninvasive, low risk alternative for iron assessment, and therefore more acceptable to patients and providers.

The liver R2-MRI study impacted clinical care in our patient population, with adjustments in chelation therapy or transfusion method following at least one-third of MRI studies. The R2-MRI results also served to reinforce continuation of current care and as a platform to address adherence. Specific documentation of R2-MRI findings and management decisions

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greatly improved over the study period, likely reflecting improved provider familiarity with the technology. A significant reduction in LIC between the first and final liver R2-MRI studies with a greater proportion of LIC below 7 ng/g dw supports a benefit from LIC monitoring. These findings point to important progress in a patient population that historically does not receive optimal monitoring of iron overload.[13] The utility of the serum ferritin, alone, in the management of patients with SCD is questionable. In our cohort, serum ferritin levels below 1,500 ng/ml and above 2,500 ng/ml generally predicted acceptable and unacceptable LIC, respectively, but ferritin levels of 1,500 to <2,500 ng/ml were associated with widely variable LIC. These findings are consistent with prior research [19,20] and taken together support the utility of annual R2-MRI assessment especially when the ferritin level is above 1,500 ng/ml.

Our data confirm the value of erythrocytapheresis to prevent or reduce iron loading in individuals with SCD.[12] Among subjects who never received simple transfusions, ferritin remained in an acceptable range and chelation was never required; early institution of erythrocytapheresis was therefore effective at minimizing iron burden. However, the need for adequate intravenous access may limit the ability to utilize erythrocytapheresis, especially in young children. In our cohort, the median age of initiation of erythrocytapheresis was 9.9 years, and 15 subjects required CVLs for erythrocytapheresis. Importantly, our data show that patients who initially received simple transfusion had significant improvement in iron burden upon switching to erythrocytapheresis. Many of these patients either did not receive or were able to discontinue chelation therapy. These potential benefits of well-controlled iron burden must be weighed against the limitations of erythrocytapheresis, which also include increased donor exposure. Thealloimmunization rate was high across our entire study population, likely explained in part by RH variability within both us and our donor and recipient pools,[21] but highest among children receiving exchange transfusions. Additionally, availability of adequate expertise limits universal access to erythrocytapheresis therapy.

Not surprisingly, in our SCD cohort deferasirox is the predominantly prescribed chelating agent. Since the drug became clinically available in 2006, only two children were initially prescribed deferoxamine. Nonetheless, several children switched from deferasirox to deferoxamine due to adverse effects or poor control of iron burden. Whether the recent availability of a film-coated tablet formulation will make deferasirox more tolerable remains to be seen. Due to the small numbers of subjects receiving deferoxamine, direct comparison of change in iron burden on different chelating agents was not possible. Good adherence with either chelator agent correlated with better ferritin and LIC, which supports the need to routinely assess adherence and barriers to adherence.

Limitations of the study include reliance upon documentation of patient report for assessment of adherence, which can be unreliable, influenced by provider bias, and inconsistently documented. Additionally, this study analyzed patients at a Comprehensive Sickle Cell Center with an apheresis unit, a comprehensive care team, and R2-MRI, resources that may not be available at many other centers and may limit the study’s generalizability. However, we believe our data support the expansion of access to these tools throughout the SCD care community.

In summary, increased availability of iron assessment through R2-MRI and of oral chelation paralleled improved management of iron overload in our population with SCD, similar to what has been reported in the patient population with thalassemia.[4] Serum ferritin has significant limitations in assessment of iron burden in children with SCD, and liver iron assessment therefore is necessary for optimal management. The effectiveness of erythrocytapheresis in preventing or reducing iron burden in our SCD population, even with significant iron loading after periods of simple transfusion, was confirmed. Limiting the duration of chronic simple transfusion therapy and encouraging adherence to chelation therapy are important strategies to control iron overload and its associated clinical consequences.

REFERENCES
1. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005;353:2769–2778.
2. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallacher D, Kutlar A. Non-alternative, non-chelation treatment alternatives: a proactive approach to non-chelation treatment alternatives in the perioperative management of sickle cell disease. Transfusion 2004;44:1971–1978.
3. Vichinsky E, Butenkos E, Fang E, Hudes M, Theil E, Ferrell L, Williams R, Loutie L, Lee PD. Hartzman P. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. Ann J Hematol 2005;80:76–84.
4. Wood JC, Tyiska M, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2006;103:1934–1936.
5. Kim HC, Dagnan NF, Silber JH, Martin MB, Schwartz E, Ossias J, Konarogiro-Lagana M. Impact of magnetic resonance imaging on cardiac mortality in thalassemia major. J Magn Reson Imaging 2003;18:345–349.
6. Fung EB, Hartzman P, Lee PD, Milet M, Beliveau R, Jeng MR, Kalinyak KA, Hudes M, Bhatai S, Vichinsky EP. Increased prevalence of iron overload associated endocrineopathy in thalassemia major and sickle cell disease. Br J Haematol 2006;135:374–382.
7. Vichinsky E, Butenkos E, Fang E, Hudes M, Theil E, Ferrell L, Williams R, Loutie L, Lee PD. Hartzman P. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. Ann J Hematol 2005;80:76–84.
8. Wood JC, Tyiska M, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2006;103:1934–1936.
9. Kim HC, Dagnan NF, Silber JH, Martin MB, Schwartz E, Ossias J, Konarogiro-Lagana M. Impact of magnetic resonance imaging on cardiac mortality in thalassemia major. J Magn Reson Imaging 2003;18:345–349.
10. Fung EB, Hartzman P, Milet M, Beliveau R, Jeng MR, Kalinyak KA, Hudes M, Bhatai S, Vichinsky EP. Increased prevalence of iron overload associated endocrineopathy in thalassemia major and sickle cell disease. Br J Haematol 2006;135:374–382.
11. Vichinsky E, Butenkos E, Fang E, Hudes M, Theil E, Ferrell L, Williams R, Loutie L, Lee PD. Hartzman P. Comparison of organ dysfunction in transfused patients with SCD or beta thalassemia. Ann J Hematol 2005;80:76–84.
12. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassemia major in the UK and related to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2008;10:42.
13. Chonkar O, Gershman J, Pharoah POD, Walshe J. Impact of heart magnetic resonance imaging on chelation choices, compliance with treatment and risk of heart disease in patients with thalassemia major. Br J Haematol 2013;163:400–405.