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Red blood cell transfusion therapy for sickle cell patients with frequent painful events

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Abstract

Background: Recurrent pain events or chronic pain are among the most common complications of sickle cell disease. Despite attempts to maximize adherence to and dosing of hydroxyurea, some patients continue to suffer from pain. Our institution developed a program to initiate chronic red blood cell transfusions for one year in patients clinically deemed to have high healthcare utilization from sickle cell pain, despite being prescribed hydroxyurea.

Procedure: An institutional review board approved retrospective study to evaluate the health outcomes associated with a one-year red blood cell transfusion protocol in sickle cell patients experiencing recurrent pain events as compared with the health outcomes for these patients in the one year prior to receiving transfusion therapy. We performed a matched-pair analysis using a Wilcoxon signed rank to determine the impact of transfusion therapy on clinic visits, emergency department visits, hospital admissions, hospitalization days, and opioid prescriptions filled.

Results: One year of transfusion therapy significantly reduced the number of total emergency department visits for pain (6 vs 2.5 pain visits/year, $P = 0.005$), mean hospitalizations for pain (3.4 vs 0.9 pain admissions/year), and mean hospital days per year for pain crisis (23.5 vs 4.5, $P = 0.0001$), as compared with the one year prior to transfusion therapy. We identified no significant difference in opioid prescriptions filled during the year of transfusion therapy.

Conclusion: Patients with frequent pain episodes may benefit from one year of transfusion therapy.

KEYWORDS

outcomes, pain, sickle cell anemia, transfusion

1 | INTRODUCTION

Acute vaso-occlusive pain crisis is a hallmark symptom for patients with sickle cell disease. Some sickle cell patients develop recurrent episodes of acute vaso-occlusive pain each year or progress to chronic pain requiring frequent daily opioid administration.[1] Hydroxyurea is FDA approved in pediatrics and adults to reduce the frequency of these vaso-occlusive pain events and prevent hospitalizations; however, many adult patients with frequent sickle cell pain-related events are not receiving hydroxyurea.[2] Among those prescribed hydroxyurea, aggressive titration to maximal tolerated dose and strict adherence may provide additional benefits for pain outcomes.[3–5] However, limited data exist that examine outcomes for hydroxyurea in patients who progress to recurrent vaso-occlusive pain crisis or chronic pain. In a randomized, placebo-controlled phase II adult sickle cell study of crizanlizumab in patients with two to ten pain crises per year at baseline, 40 patients randomized to placebo and hydroxyurea developed a median of 3.58 pain crises per year while on study, which was higher than their baseline event rate of 2.98 pain crises per year.[6] These data suggest that even during a well-designed clinical trial, patients with recurrent episodes of acute vaso-occlusive pain administered hydroxyurea therapy may continue to have frequent need for healthcare utilization. Additional important nonpharmacological treatments for pain are increasingly recognized and include an intensive multidisciplinary approach that incorporates self-efficacy, cognitive behavioral therapy,

Abbreviation Key: ED, emergency department; OME, oral morphine equivalents; VOC, vaso-occlusive pain crisis

guided imagery, and catastrophizing management.[7–9] However, the availability of resources to support these multidisciplinary approaches likely limits their widespread adoption.

Chronic transfusion therapy offers another possible treatment for patients with frequent pain events.[10–15] However, data investigating the effectiveness of this intervention for recurrent pain are limited. Current data for the effectiveness of transfusions in pediatrics are derived via secondary data analyses from clinical trials that initiated transfusion therapy for primary or secondary prevention of overt and/or silent stroke. Minimal data exist for the effectiveness of transfusion therapy in patients who initiated transfusions specifically for pain as the indication. To address this knowledge gap, we conducted a retrospective analysis of our institution's transfusion program for pain. We initiate chronic red blood cell transfusions for one year in patients clinically deemed to have high healthcare utilization from sickle cell pain, with minimal response to other therapies. We hypothesized that monthly red blood cell transfusion therapy for one year would reduce healthcare utilization for pain, decrease reliance on opioid prescriptions for pain management, and improve healthcare economics.

2 | METHODS

2.1 | Study population

We conducted an institutional review board-approved, retrospective study to evaluate the health outcomes associated with a one-year red blood cell transfusion protocol in sickle cell patients experiencing recurrent pain events as compared with the health outcomes for these patients in the one year prior to receiving transfusion therapy. We identified patients from 2012 to 2016 who received one year of transfusion therapy for an indication of recurrent pain in our University of Alabama at Birmingham Pediatric Sickle Cell clinical database. The decision to offer transfusion therapy to reduce frequent pain events was at the sole discretion of the attending physician. The decision to accept transfusion therapy relied on joint decision-making to incorporate family preferences and treatment burden. As patients with frequent pain events frequently accepted red blood cell transfusion therapy, we were unable to identify a control group of patients offered transfusion therapy for frequent pain but refused. All patients were scheduled to receive simple red blood cell transfusion every 4 weeks with a goal to maintain a percent sickle hemoglobin level between 30% and 50% and target a posttransfusion Hct of 32% and 34%. As standard of care, we perform minor antigen matching for all red cell transfusions in sickle cell patients. Hydroxyurea therapy could be continued during the one year of transfusion therapy based on joint decision-making between the physician and family.

2.2 | Clinical investigation

Electronic medical records were reviewed to obtain data on health outcomes from one year prior to the initiation of transfusion therapy and one year post red blood cell transfusion therapy. Our primary outcome was to evaluate the impact of one-year blood cell transfusion therapy on emergency care utilization and hospitalizations for pain; data extracted included total number of clinic visits per year, emergency department (ED) visits (total visits and visits for pain crisis as the chief complaint), hospitalizations (total and pain crisis as the primary admission diagnosis), and total number of hospital days per admission. We identified two patients with clinic notes documenting admission to an outside hospital for pain crisis, but we were unable to obtain medical records to confirm the number of hospital days. Therefore, we included the two hospital admissions in the total number of hospitalizations per year but excluded that admission from analysis of hospital days per admission. To evaluate alloimmunization, we extracted records for a positive antibody screen and subsequent identification of a specific antibody or nonspecific antibody by the Children's of Alabama blood bank. Ferritin levels from the 12-month visit and a liver iron content value estimated by T2* liver MRI within 3 months prior to or 6 months post their 12 month transfusion visit were recorded to document iron overload.

A secondary outcome was to evaluate the impact of chronic red cell transfusion on prescription opioid use. We used prescribed opioid quantity as a surrogate marker since we could not measure the actual quantity of opioid therapy used by the patient. We extracted data from the Alabama Prescription Drug Monitoring Program website on opioid prescription quantity and doses of opioids dispensed during the two-year study period. We calculated the oral morphine equivalents (OME) for each drug to be 0.15, 1, 4, 1, and 1.5 mg for codeine, hydrocodone, hydromorphone, morphine, and oxycodone, respectively, via the www.globalrph.com opioid analgesic converter. The OME for three patients could not be determined, as data prior to November 2012 were not available on the Physician Drug Monitoring Program website.

Finally, we were interested in the health economics associated with a one-year transfusion protocol for patients with frequent pain events. We imputed hospital costs using 2014–2015 claims data from the Alabama Children's Health Insurance Program, ALL Kids. ALL Kids contracts with Blue Cross/Blue Shield (BCBS) of Alabama (the single largest insurer in the state) for claims processing and access to BCBS provider networks and fee schedules. Based on inpatient claims data from 20 unique enrollees with one or more sickle cell pain hospitalizations (annual hospital days range, 1–30), the calculated average cost for one inpatient day was $2202. Next, we obtained cost from the outpatient clinic charges directly from the financial office at Children's of Alabama. We calculated the mean cost for a hydroxyurea clinic visit ($686/visit) and transfusion visit ($1505/visit) at Children's of Alabama. At our institution, the transfusion costs include performing extended phenotype matching and transfusing two units of packed red blood cells.

2.3 | Statistical analysis

To describe the characteristics of these patients, we calculated counts and percentages for categorical variables and means, standard deviations, and ranges for continuous variables. To analyze the impact of transfusion to reduce ED visits, hospitalizations, hospitalization

days, clinic visits, and OME prescribed, we performed a matched-pair analysis using a Wilcoxon signed-rank test to account for possible nonnormal distribution of data in this small study. JMP 13 (Cary, NC) was used for this analysis.

3 | RESULTS

We identified 14 participants initiated on chronic transfusion therapy for one year to reduce frequent pain events. Eight patients (57%) were male. The mean age at initiation of transfusion therapy was 13.6 years. All patients were previously prescribed treatment with hydroxyurea before initiation of transfusion therapy. The mean hemoglobin F level at the initiation of transfusion therapy was 10% (range, 1.3%–26.9%) and the mean MCV was 85 fL (range, 76.6–124.6 fL). Eleven of the 14 participants remained on hydroxyurea while receiving transfusion therapy. The mean ferritin measurement for all 14 patients at 12 months of transfusion therapy was 1343 ng/mL (SD, 610 ng/mL) and the mean LIC for 8 patients who underwent iron overload imaging was 4.3 mg/g of dry tissue (SD, 2.5 mg/g of dry tissue). Among the 14 patients, two patients were identified with alloimmunization prior to starting transfusion therapy for pain (one: anti-Jsa and one: anti-C, Jka, E), one patient developed a nonspecific antibody during the one year of transfusion therapy, and two developed a nonspecific antibody after one year of transfusion therapy.

One year of transfusion therapy significantly reduced the mean number of total ED visits (6 vs 2.5 visits/year, $P = 0.005$), mean ED visits for pain (6 vs 2.5 pain visits/year, $P = 0.005$), mean total number of hospitalizations (3.5 vs 1 admissions/year, $P = 0.0002$), and mean hospitalizations for pain (3.4 vs 0.9 pain admissions/year) as compared with the one year prior to starting transfusion therapy (Figure 1). One year of transfusion therapy significantly decreased the mean total hospital days per year for pain crisis (23.5 vs 4.5, $P = 0.0001$) while the mean hospital days per each admission nonsignificantly decreased (7.4 vs 4.2 days per admission, $P = 0.17$) as compared with the one year prior to transfusion therapy. As expected, one year of red cell transfusion therapy every four weeks resulted in a significant increase in clinic visits (4–13 clinic visits/year, $P = 0.0001$) as compared with the one year prior to initiating transfusion therapy. The OME prescribed for patients prior to and during one year of transfusion therapy was not significantly different (2400 vs 2636 oral morphine equivalents/year).

The estimated cost of an inpatient hospital day was $2202, the estimated cost for a hydroxyurea clinic visit was $686, and the estimated cost of a transfusion visit was $1505. For the year prior to transfusion therapy, the cost for a mean of 23.5 hospital days was $51 747 and the cost for a mean of 4 hydroxyurea clinic visits was $2744. Therefore, the estimated total healthcare cost was $54 491 in the one year prior to transfusion. During one year of transfusion therapy, the cost for a mean of 4.5 hospital days was $9909 and the cost for a mean of 13 transfusion clinic visits was $19 565. Therefore, the estimated total healthcare cost was $29 474 during the one year of red cell transfusion therapy. The estimated savings for one year of transfusion therapy in our patient population with recurrent pain events was $25 017.

4 | DISCUSSION

Sickle cell patients with frequent pain events require multimodal interventions to improve their quality of life. These data suggest a chronic transfusion therapy protocol for patients with frequent pain can significantly reduce healthcare utilization among this high-risk population and improve healthcare economics. While this transfusion program significantly reduced the number of ED visits and hospitalizations for pain, this study did not identify that one year of transfusion therapy reduced the number of OME prescribed to each patient in one year. One possible reason for failing to reduce opioid use is that patients who have transitioned to a chronic pain syndrome may continue to have pain despite reduction of their sickle hemoglobin. This suggests that pain may be driven by factors outside of the red blood cell and occur at the level of the peripheral and/or central nervous system and one year of chronic red cell transfusion therapy likely does not reverse this process.[16,17] This concept is corroborated by data post bone marrow transplantation where patients continue to require opioid medications after this curative therapy.[18] A second possibility is that we used a surrogate marker of opioid prescription quantity filled rather than utilized. This finding may be relevant for patients with frequent pain who continued to request opioid prescriptions at each clinic visit for transfusion for management of their pain at home. Finally, while we did not capture school attendance and quality of life, based on prior literature we could hypothesize that both of these important patient-centered measures would improve during transfusion and are part of the joint therapeutic decision-making.[19]

While transfusion therapy may improve healthcare utilization, obvious potential complications of alloimmunization or iron overload could obviate patient preference for continuation of transfusion therapy after one year. Despite discussions about the potential for alloimmunization and need to initiate iron chelation, several patients in our cohort elected to remain on transfusion therapy after the 12-month period including 6 patients who have been on transfusion therapy for over two years. While only one patient developed an antibody during the first 12 months of transfusion therapy, two additional patients developed an antibody after that time. Second, the mean HbF of 10% at initiation of red cell transfusion in our study population suggests that despite frequent pain and need for hospitalization, adherence to an oral therapy was suboptimal in this cohort. Among patients with a history of poor adherence to hydroxyurea, chronic transfusion therapy could introduce a clinical risk for iron overload for patients that are nonadherent to iron chelation. This cohort further demonstrated that at 12 months of transfusion therapy, sickle cell patients should begin iron chelation therapy and iron overload monitoring. The initiation of iron chelation therapy and performing imaging procedures to monitor iron overload will introduce additional costs not covered in this analysis. The risks and costs of alloimmunization and iron overload during longer-term transfusion therapy for recurrent pain needs to be further studied in order to provide comprehensive data for shared decision-making.

These data suggest a clinical benefit to transfusion therapy for patients with recurrent pain crises; however, there are some limitations worth noting. First, we could not determine in this retrospective

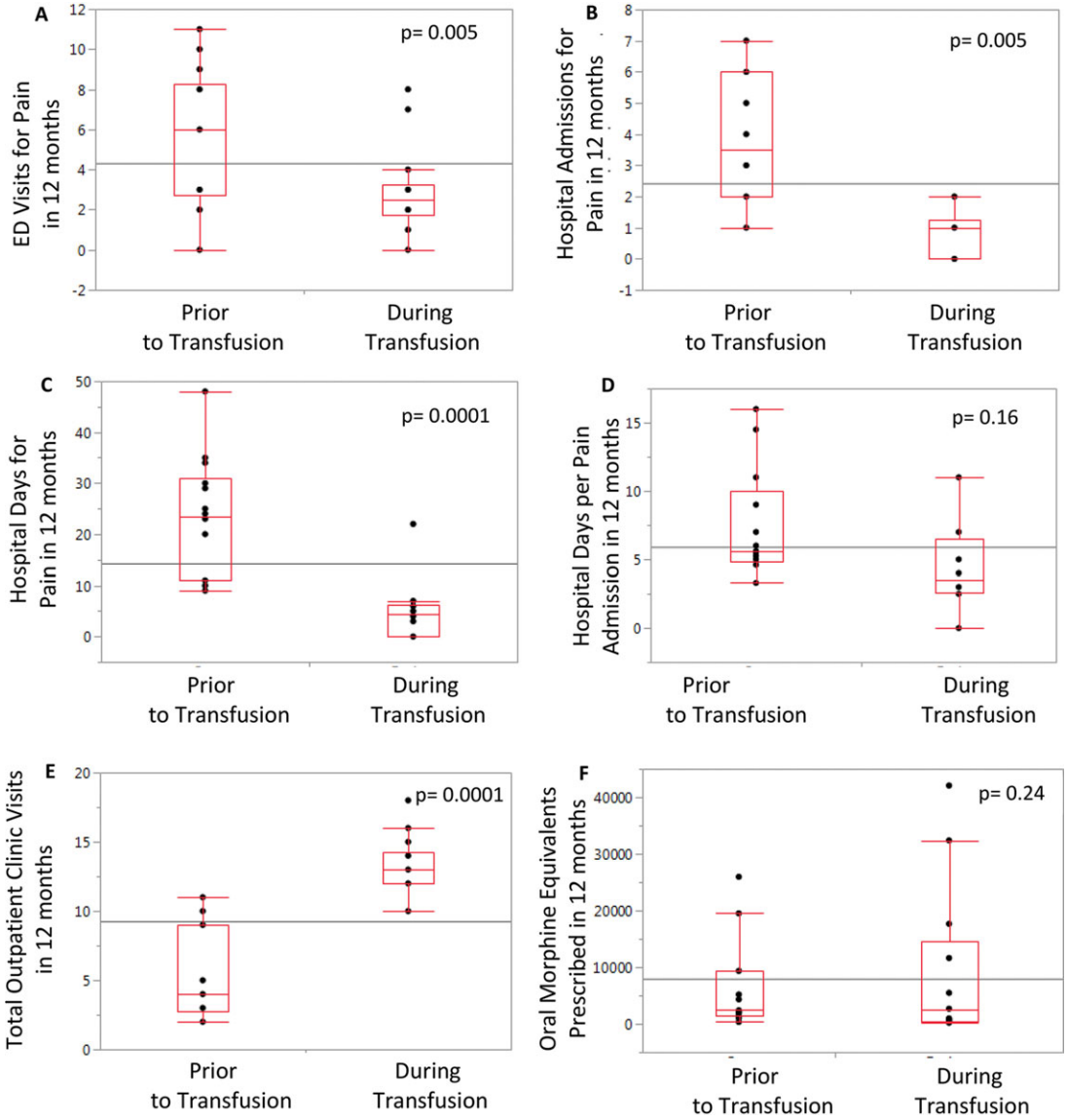

FIGURE 1 Comparison of outcomes for 12 months prior to starting transfusion therapy and 12 months during transfusion therapy for (A) ED visits for pain in 12 months, (B) hospital admissions for pain in 12 months, (C) hospital days for pain in 12 months, (D) hospital days per admission for pain in 12 months, (E) total outpatient clinic visits in 12 months, and (F) OME prescribed in 12 months

study the frequency of days with home pain or changes in the intensity of pain, which could provide additional data on the potential benefit of transfusion. Second, we did not obtain data on psychological comorbidities that contribute to frequent pain events including depression, anxiety, and poor sleep. In addition, we could not account for a positive relationship between frequent interactions with healthcare providers and a decrease in need for emergent healthcare utilization as patients were scheduled for transfusion every four weeks. Finally, we could not account for various out-of-pocket expenses for the costs of medications, clinic visits, or hospitalizations based on different insurance company policies, as well as the costs of travel to the clinic, childcare expenses, or missed days from work. For patients who continued on transfusion therapy after 12 months, several additional costs of healthcare to consider include the costs of chelation therapy, institutional iron overload monitoring, and potential costs for placing a central venous line and performing exchange transfusion therapy.

In conclusion, despite concerns for iron overload, infection, and alloimmunization inherent in a red blood cell transfusion protocol, patients with frequent pain episodes who are nonresponsive to hydroxyurea may benefit from one year of transfusion therapy. Future studies should include the impact of transfusion therapy on quality of life, missed school days, iron overload and alloimmunization to more fully assess the effects of transfusion on difficult to manage pain and determine the balance between benefit and risk.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report relevant to this study.

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