REGULAR ARTICLE

blood advances

Economic evaluation of regular transfusions for cerebral infarct recurrence in the Silent Cerebral Infarct Transfusion Trial

Peter Hsu,[1] James C. Gay,[1] Chyongchiou J. Lin,[2] Mark Rodeghier,[3] Michael R. DeBaun,[4] and Robert M. Cronin[5]

[1]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN; [2]College of Nursing, The Ohio State University, Columbus, OH; [3]Rodeghier Consultants, Chicago, IL; [4]Vanderbilt-Meharry, Center of Excellence in Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN; and [5]Department of Internal Medicine, The Ohio State University, Columbus, OH

Key Points

- Children with preexisting silent cerebral infarcts on regular transfusion therapy had 50% lower hospitalization costs than standard care.
- The incremental cost-effectiveness ratio for transfusion therapy to prevent infarct recurrence was $22 025 for every infarct prevented.

In 2020, the American Society of Hematology published evidence-based guidelines for cerebrovascular disease in individuals with sickle cell anemia (SCA). Although the guidelines were based on National Institutes of Health–sponsored randomized controlled trials, no cost-effectiveness analysis was completed for children with SCA and silent cerebral infarcts. We conducted a cost-effectiveness analysis comparing regular blood transfusion vs standard care using SIT (Silent Cerebral Infarct Transfusion) Trial participants. This analysis included a modified societal perspective with direct costs (hospitalization, emergency department visit, transfusion, outpatient care, and iron chelation) and indirect costs (special education). Direct medical costs were estimated from hospitalizations from SIT hospitals and unlinked aggregated hospital and outpatient costs from SIT sites by using the Pediatric Health Information System. Indirect costs were estimated from published literature. Effectiveness was prevention of infarct recurrence. An incremental cost-effectiveness ratio using a 3-year time horizon (mean SIT Trial participant follow-up) compared transfusion vs standard care. A total of 196 participants received transfusions (n = 90) or standard care (n = 106), with a mean age of 10.0 years. Annual hospitalization costs were reduced by 54% for transfusions vs standard care ($4929 vs $10 802), but transfusion group outpatient costs added $22 454 to $137 022 per year. Special education cost savings were $2634 over 3 years for every infarct prevented. Transfusion therapy had an incremental cost-effectiveness ratio of $22 025 per infarct prevented. Children with preexisting silent cerebral infarcts receiving blood transfusions had lower hospitalization costs but higher outpatient costs, primarily associated with the oral iron chelator deferasirox. Regular blood transfusion therapy is cost-effective for infarct recurrence in children with SCA. This trial is registered at www.clinicaltrials.gov as #NCT00072761.

Introduction

Sickle cell disease is the most common abnormality detected on newborn screening,[1] affecting 1 in 375 African-American subjects[2,3] and almost 90 000 individuals overall in the United States.[4] The more severe forms of sickle cell disease (hemoglobin SS, hemoglobin $S\beta^0$ thalassemia), referred to as sickle cell anemia, occur in 1 in 400 African-American newborns.[3] Sickle cell anemia–related neurologic morbidity from cerebrovascular complications can be severe. The most common cause of permanent

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neurologic injury in children and adults with sickle cell anemia is a silent cerebral infarct, occurring in ~39% of children by age 18 years.[5] Silent cerebral infarcts require magnetic resonance imaging (MRI) to detect and a formal neurologic examination to exclude the presence of an overt stroke.[6] Silent cerebral infarcts are progressive in both children[7,8] and adults.[9,10] Silent cerebral infarcts are associated with at least a 5-point full-scale intelligence quotient drop in children,[11] and with biologically plausible evidence to indicate a similar degree of neurologic morbidity in adults. Once silent cerebral infarcts are identified, children and adults are eligible for evaluation for Individualized Education Plans and Americans with Disability Act services, respectively. Most silent cerebral infarcts occur in the brain's border zone regions, including the frontal lobe,[12] which disproportionately affect executive function. The American Congress of Rehabilitation Medicine has formally endorsed evidence-based strategies to support individuals with executive dysfunction.[13]

In 2020, the American Society of Hematology (ASH) published evidence-based guidelines for preventing, diagnosing, and treating cerebrovascular disease in children and adults with sickle cell disease.[13] The guideline panel developed clinical recommendations and assessed the certainty of the supporting evidence based on evidence-to-decision factors using the Grading of Recommendations, Assessment, Development and Evaluations approach.[14-17] The evidence-to-decision factors, which determined the clinical guideline recommendations, ask for an assessment of the effects of interventions and resource utilization (cost-effectiveness), among others. Although the effects of stroke prevention interventions were based on 5 completed National Institutes of Health–sponsored randomized controlled trials, no assessment of resource utilization has been performed in the SIT (Silent Cerebral Infarct Transfusion) Trial to accompany the benefits of regular blood transfusions to prevent cerebral infarct recurrence. This lack of cost-effectiveness evaluation is a gap in the current ASH guidelines for treating children with preexisting silent cerebral infarcts. To fill this gap in informed decision-making regarding the treatment of silent cerebral infarcts with regular blood transfusion therapy, we conducted a cost-effectiveness analysis of blood transfusion therapy to prevent cerebral infarct recurrence in children with preexisting silent cerebral infarcts participating in the SIT Trial.

Regular blood transfusion therapy significantly reduced recurrent cerebral infarcts in children with sickle cell anemia in the SIT Trial.[7] Regular blood transfusion therapy is costly, burdensome, and associated with an increased iron burden and iron overload–associated morbidity. Furthermore, the impact of lowering the incidence of silent and overt strokes in sickle cell anemia on costs related to other aspects of the lives of individuals with sickle cell (eg, education) remained unanswered. We performed a cost-effectiveness analysis to address a critical gap in understanding the tradeoffs between monthly blood transfusions vs standard care to prevent infarct recurrence (silent or overt stroke) in children with preexisting silent cerebral infarcts. We included the costs associated with medical care (hospitalization, emergency department visit, transfusion, and outpatient care) and indirect costs of special education.

Materials and methods

Parent study

The current analyses were conducted as a secondary aim of the SIT Trial.[7] The trial's primary aim was to determine whether regular blood transfusion therapy reduced overt stroke incidence and new or worsening silent cerebral infarcts among children with sickle cell anemia and a history of silent cerebral infarcts. Children aged 5 to 15 years with sickle cell anemia (defined as hemoglobin SS or hemoglobin $S\beta^0$ thalassemia) were enrolled from 3 December 2004, to 3 December 2010, with all follow-up completed as of 29 July 2013. After a screening MRI to exclude children without prior silent cerebral infarct, study candidates underwent transcranial Doppler screening. Children whose transcranial Doppler result was above the transfusion threshold (nonimaging method, ≥200 cm/sec; imaging method, ≥185 cm/sec) were excluded. Eligible children underwent a full MRI protocol immediately before randomization, including optional magnetic resonance angiography. We recorded the primary reason for hospitalization and the length of stay for each participant during the trial.

The institutional review board approved the SIT Trial at each participating institution. The SIT Trial is registered at www.clinicaltrials.gov (#NCT00072761). The study was conducted in accordance with the Declaration of Helsinki.

Intervention

In the original trial, 196 children were randomly assigned to receive standard care (herein referred to as the standard care group) or regular blood transfusions (herein referred to as the transfusion group) for at least 36 months or until a study end point was reached. Participants who were randomly assigned to the standard care group received no treatment of silent infarcts, including no hydroxyurea therapy. They were seen biannually as outpatients with complete blood count laboratory testing. Participants in the transfusion group received either automated exchange transfusion (recommended) or simple or partial exchange transfusion (acceptable), initially at 2-week intervals until the hemoglobin S levels were reduced to 30% or lower and at 4-week intervals after that. Participants in the transfusion group also received regular iron chelation therapy to reduce complications associated with transfusion-related iron overload. For the current study, the transfusion group was determined by using a protocol approach, with all participants included who received regular transfusions over at least 6 months, irrespective of the original group assignment.

Descriptive analyses were performed for demographic characteristics and clinical features of participants in the SIT Trial. Means and standard deviations are reported for continuous variables, and proportions are reported for categorical variables. Various statistical tests, including the Mann-Whitney U test, χ^2 test, mid-P exact test, and permutation test, were performed to compare those variables between the standard care and transfusion groups. Statistical analyses were conducted by using SPSS version 26 (IBM SPSS Statistics, IBM Corporation), and statistical significance was set at $P < .05$.

Outcomes and measures

The primary sickle cell anemia–related outcomes were hospitalizations at participating hospitals. Data for hospitalizations occurring at non-study hospitals were not available and thus were not considered. Based on primary discharge diagnosis, hospitalizations were categorized primarily due to the following order's hierarchical categories: acute chest syndrome (ACS), pain, fever or infection, exchange transfusion, surgery, or asthma. Follow-up occurred from

random allocation to primary end point (an overt stroke or new or progression of silent cerebral infarct) or exit MRI, whichever came first.

Cost data

Direct medical costs. Direct medical costs included hospitalizations, emergency department visits, and outpatient costs.

Hospitalizations. The Children Hospital Association's Pediatric Health Information System (PHIS) database was used to estimate costs per day of hospitalization. Currently, the PHIS database includes clinical and billing data from 49 tertiary care children's hospitals located in noncompeting markets of 27 states plus Washington, DC, accounting for ~20% of annual pediatric hospitalizations in the United States. De-identified data submitted by participating hospitals include an encrypted medical record number, which allows tracking of individuals to the same hospital over time. In addition, data quality is ensured through a joint effort between the Children's Hospital Association and participating hospitals.[18] Between 2003 and 2010, PHIS membership increased from 35 to 45 hospitals, with 14 US SIT Trial institutions (48% of the 29 SIT Trial institutions) contributing to PHIS cost estimates.

Total costs for each hospitalization were calculated by PHIS adjusted with each hospital's annual costs-to-charges ratio[19] for each year, using the Centers for Medicare & Medicaid Services wage/price index for the given hospital's location. Inpatient costs were based on length of hospital stay, modified by the occurrence of categories of adverse events in the following non-overlapping hierarchy:

1. ACS: admissions with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 517.3, without any codes for stroke.
2. Vaso-occlusive pain episodes (including avascular necrosis, headache, priapism, and acute anemia): admissions with ICD-9-CM code 282.xx, without ACS and stroke codes, and generic drug codes for opiates.
3. Fever/infection: admission with any SS disorder code without ACS and stroke codes and with 1 of 1500 ICD-9-CM infectious disease codes.
4. Exchange transfusion: admission with an ICD-9-CM code for sickle cell disorders plus procedure code for exchange transfusion.
5. Surgery: admission with an ICD-9-CM code for sickle cell disorders without ACS and stroke codes and a surgical All Patients Refined Diagnosis Related Groups code.
6. Asthma: admission with any sickle cell SS disorder code and asthma code (493.xx) without ACS and stroke codes or generic drug codes for opiates.

Our goal was to estimate the costs of hospitalizations for most participants in our cost analyses for sickle cell complications. Although the length of stay was not normally distributed, we used an established statistical calculation[20] to exclude high outliers using a cutoff of the 75th percentile (Q3) plus 1.5 times the interquartile range of the length of stay for a given participant subset. This method resulted in an overall mean length of stay cutoff of 9.5 days, with a range of 8.5 days for hospitalizations for suspected infection with a fever to 12 days for ACS. Linear regression modeling was then performed on the total cost per hospitalization vs length of stay graph to develop a cost per day for each adverse event type.

Inpatient costs were projected to be 54.3% lower ($4929 vs $10 802 per year) for the transfusion and standard care groups, respectively, correlating with the reduction in annual length of stay. Reported estimates for professional fees ranged between 17.7% and 26.4% of facility costs of hospitalization.

Emergency department visits. Costs for emergency department visits for vaso-occlusive pain episodes and ACS were developed by using a similar clinical algorithm for hospitalizations. The 14 PHIS hospitals represented in the SIT Trial were queried for emergency department encounters for vaso-occlusive pain episodes and ACS in 2020. The mean and standard deviation cost for each encounter type were calculated.

Outpatient services. We included outpatient medical expenses from the PHIS and available literature for transfusion, including physician costs, laboratory tests, surveillance, and expenses for blood transfusions. Physician cost for an outpatient visit was estimated based on work relative value units for a Current Procedural Terminology code of 99215 (2.80) and compensation per work relative value units ($36.09).[21] A laboratory test for a complete blood count was $7 from the Centers for Medicare & Medicaid Services clinical laboratory fee schedule.[22] An annual liver iron content scan was between $400 reported by Wood et al[23] to $5865 based on costs from a PHIS site. Costs of blood transfusions were estimated from several sources.[24,25] Costs for blood transfusion estimates ranged from $616 to $1706 for transfusion of 2 units of packed red blood cells by simple transfusion or partial exchange. Costs for therapeutic erythrocytapheresis (herein referred to as apheresis) were obtained from a participating SIT center. Apheresis costs were $3452 per procedure and $44 871 annually.

Iron chelation costs were based on a child who weighed 29 kg (median weight among participants in the SIT Trial) and received deferasirox, an oral iron chelator, at the standard dose of 20 mg/kg per day. We used deferasirox for our base case because this iron chelation agent is the first-line assessment for iron chelation therapy for regular transfusion therapy in sickle cell anemia. Given the typical tablet size for deferasirox (500 mg), we used this for the daily dose estimate for the mean study participant for oral iron chelation. Costs for a 500-mg tablet of generic deferasirox ranged from $112 to $192 as obtained from Lexicomp.[26] The mean of the low and high end of the range ($152 per tablet) was used for the base case, yielding a yearly cost of $55 440. We also obtained deferoxamine cost as an alternative or additional iron chelation therapy. A 500-mg vial of deferoxamine cost was obtained from the pharmacy at participating SIT centers ($13.45). Costs of home administration of subcutaneous deferoxamine were $28 per day as estimated in consultation with a home infusion company serving a participating center. Based on these estimates, the cost of deferoxamine was $11 008 per year.

Indirect costs of special education. Participants with silent cerebral infarcts and overt strokes endure a range of disabilities that incur additional costs compared with participants without such events. Using data from the academic year of 1999 to 2000, and

adjusting for inflation,[27] other education expenditures for a student with a cerebral infarct range from $16 359 to $31 134 per year depending on the degree of their disabilities (mean for our base case, $23 746 per year).[28] Among children with sickle cell anemia, 28.8% without cerebral infarcts and 74.6% with cerebral infarcts would need special education.[29] For these differences in education costs, the potential savings would be $14 384 per year for every cerebral infarct prevented. In the SIT Trial, 6 (6%) participants in the transfusion group had cerebral infarct recurrence, and 16 (14%) had infarct recurrence in the standard care group. Therefore, the annual cost of special education would be $7402 for the transfusion group and $8280 for the standard care group, yielding a savings of $2634 over the 3-year time horizon.

Cost-effectiveness analysis

We took a modified societal perspective in the current analysis. A simple incremental cost-effectiveness ratio was performed by using costs expected over a 3-year time horizon, the mean follow-up duration of the SIT Trial participants. The incremental cost-effectiveness ratio was defined according to the difference in costs between the 2 treatment groups (transfusion group vs standard care group) divided by the difference in their effectiveness. The cost, measured in terms of dollars, was calculated as described in the collection/estimation of cost data in the "cost data" section of the methods above. Costs were adjusted for inflation and expressed in 2020 US dollars.[27] The effectiveness was measured as infarct recurrence in children with preexisting silent cerebral infarcts.[7,30,31]

Assumptions. Cost calculations were estimated based on the existing data. We used the mean of the low and high values for direct costs of outpatient liver iron content scans, outpatient transfusions, apheresis, and outpatient iron chelation and indirect costs of special education for our base case. We assumed individuals in the transfusion group were seen monthly, and individuals in the standard care were seen every 6 months. Total cost estimates for transfusions and apheresis procedures were based on assumptions of a frequency of every 4 weeks (13 treatments per year). We used $750 and $2000 for low and high cost estimates of red blood cell transfusion, yielding $9750 to $26 000 yearly costs for blood transfusions. The mean cost of transfusion for the base case, including deferasirox as the iron chelation agent and the proportional contribution of participants receiving a simple transfusion, manual exchange transfusion, and automated exchange transfusions, was $76 864 per year.[32]

The societal perspective typically comprises all direct and indirect costs of illness, including but not limited to lifetime loss wages. However, few data are available on the indirect costs to families of students with sickle cell disease, particularly over a short duration of 3 years. Hence, we used direct medical costs and only educational costs attributable to sickle cell disease and strokes as a first approximation of societal cost.

Sensitivity analyses. We performed sensitivity analyses using the range of related outpatient liver iron content scans, outpatient transfusions, apheresis, and outpatient iron chelation as described earlier. These total yearly costs for participants in the transfusion group ranged from $22 454 to $137 022, depending on the estimated costs for the type of iron chelation used and kind of red blood cell transfusion (manual partial exchange or apheresis). These estimates included costs of transfusions with and without red blood cell alloimmunization. As part of the sensitivity analyses, we also included the range of special education costs depending on the degree of disabilities described earlier.[28]

Results

A total of 196 participants received transfusions (n = 90) or standard care (n = 106) per protocol. Table 1 summarizes the demographic characteristics and the clinical features of children who participated in each group. The mean follow-up for individuals who did or did not receive blood transfusion therapy was 3.04 and 3.01 years, respectively. The mean age of all participants at randomization was 10.0 years, with 43.4% male subjects. The number of SIT Trial participants who had cerebral infarct recurrence in the transfusion and standard care groups was 6 and 16. Fifteen participants initially randomly allocated to the transfusion group crossed over to the standard care group by either never receiving blood transfusion (n= 9) or receiving <6 months of regular blood transfusion (n=6) and were counted as not being effectively transfused (ie, part of the standard care group). The main reasons for not remaining in the assigned group were based on parent decisions to forgo regular blood transfusion therapy. Red blood cell alloimmunization, the financial burden to the family, and the refusal of the health insurance company to pay for regular blood transfusion therapy were not reasons for switching from transfusion to the standard care group. The primary end point, neurologic examination and MRI of the brain, was ascertained in 94% (185 of 196) of the participants. A total of 3236 transfusions were administered in the transfusion group, and 9 alloantibodies were detected in 4 participants (anti-C [in 2 participants], anti-V [in 2 participants], anti-FyA, anti-e, anti-S, anti–JK-b, and anti-Wra), for a red blood cell alloimmunization rate of 0.278 per 100 units of red blood cells. No delayed hemolytic transfusion reactions were observed. No alloantibodies were detected among participants in the standard care group. The minor red blood cell antigen matching dramatically limited the rate of red blood cell alloimmunization and was not clinically significant in the 90 participants receiving >3000 transfusions for a median of 3 years.

Hospitalizations and length of stay

A total of 144 and 269 hospitalizations occurred in the transfusion and the standard care groups, respectively. The mean hospital length of stay was 2.5 days for the transfusion group and 3.4 days for the standard care group ($P < .001$). Participants averaged 1.6 and 2.5 hospitalizations, with a total length of stay of 358 and 912 days in the transfusion and standard care groups. On a per-patient basis, the length of stay was 53.8% lower in the transfusion group. The most common hospitalization was an acute vaso-occlusive pain episode (49.6%), followed by ACS (9.4%). Participants in the transfusion group had significantly fewer hospitalizations for vaso-occlusive pain episodes (n = 109) than those in the standard care group (n = 371) ($P < .001$), as well as fewer hospitalizations for ACS (9 vs 52; $P < .001$).

Incremental cost-effectiveness analysis

Table 2 presents annual direct medical costs and indirect costs and ranges of values used in the analysis. The mean total direct and indirect costs over the 3-year time horizon were $282 427 and $62 178 for the regular transfusion and standard care groups, respectively. The effectiveness was 6 and 16 recurrent infarcts in

Table 1. Demographic and clinical features of the 196 participants in the SIT Trial

Characteristic	Transfusion (n = 90)	Standard care (n = 106)	*P*
Age, median [IQR], y	10.0 [3.7]	9.8 [4.4]	.925*
Male sex, n (%)	33 (36.7)	52 (49.1)	.081#
No. of hospitalizations	144	269	<.001†
Length of stay, median [IQR], d	2.0 [2.0]	3.0 [3.0]	<.001*
Total length of stay (hospital days)	358	912	<.001†
Cerebral infarct incidence (per 100 patient-years)	2.0	5.6	.02‡
Hospitalizations for adverse events†			
Vaso-occlusive pain	54	151	<.001
ACS	5	34	<.001
Fever without source	12	11	.570
Fever with source	4	7	.538
Sepsis	2	0	.213
Osteomyelitis	0	2	.290
Infection	9	8	.584
Acute anemia	1	1	.923
Splenic sequestration	3	1	.303
Aplastic crisis	0	1	.538
Priapism	1	1	.923
Surgery (specialty type)	16	18	.915
Transfusion reaction, shock, oliguria, hemoglobinuria	1	0	.462
Asthma	3	5	.651
Headache	4	7	.538
Other event	29	22	.130

IQR, interquartile range.
*Mann-Whitney *U* test.
#χ^2 test.
†Mid-*P* exact test.
‡Permutation test.

the transfusion and standard care groups. The incremental cost-effectiveness ratio based on total direct and indirect costs was $22 025 per cerebral infarct recurrence prevented.

Our sensitivity analysis results estimated total direct and indirect costs for the transfusion group between $35 303 and $149 871, and the incremental cost-effectiveness ratio ranged from $4373 to $38 744 per cerebral infarct prevented. Sensitivity analyses with different indirect, special education costs changed the incremental cost-effectiveness ratio by less than $500 for every cerebral infarct prevented.

Discussion

The Grading of Recommendations, Assessment, Development and Evaluations guidelines criteria include assessing resource utilization (cost-effectiveness); however, few randomized controlled trials of sickle cell anemia include formal cost-effectiveness analysis. In 2020, the ASH published evidence-based guidelines for cerebrovascular disease in individuals with sickle cell anemia without the inclusion of formal cost-effectiveness analysis. We conducted an incremental cost-effectiveness analysis of the results of the SIT Trial. Regular blood transfusions decreased hospitalization costs and societal costs compared with standard care and had an incremental cost-effectiveness ratio of $22 025 for every cerebral infarct prevented at risk. Our findings show that regular blood transfusion therapy reduced the incidence of vaso-occlusive pain episodes (59% lower incidence) and ACS (87% lower incidence), which yields a significant reduction in hospital resource utilization as measured by the number of hospitalizations, total hospital length of stay, and costs attributed to hospitalizations. There is a concomitant increase in outpatient costs for children receiving regular blood transfusion therapy due to iron chelation costs and type of transfusion. We also report the savings in societal costs, including lower special education costs. These findings document the value of regular blood transfusions for reducing hospitalizations compared with standard care due to the prevention of adverse events beyond those involving the central nervous system.

Most families and children with sickle cell anemia would likely welcome a reduction in hospitalizations, future cerebral infarcts, and silent cerebral infarcts, along with an improvement in the child's quality of life.[33] Although no studies have shown changes in quality-adjusted life years (QALYs) for cerebral infarcts among children with sickle cell anemia, previous studies found that weighted QALYs are ~0.18 lower among adults with cerebral infarcts than in matched control subjects.[34] Future research in sickle cell anemia may explore the possibilities of measuring QALYs among young individuals.

Table 2. Annual costs of standard care and transfusion groups

Resources (2020 US$)	Transfusion (n = 90)		Standard care (n = 106)		Source of costs
	Mean ± SD	Range	Mean ± SD	Range	
Direct costs					
Hospitalization	4929 ± 7127	–	10 802 ± 15 606	–	PHIS
ED visits	–	–	–	–	PHIS
Vaso-occlusive pain visits	469 ± 301	–	1111 ± 714	–	
ACS visits	49 ± 26	–	115 ± 61	–	
Outpatient physician charges	1212	–	404	–	Centers for Medicare & Medicaid Services[21]
Outpatient complete blood count laboratory testing	84	–	14	–	Centers for Medicare & Medicaid Services[22]
Outpatient liver iron content scan	3133	400-5865	–	–	Wood,[23] PHIS site
Outpatient transfusion	21 384	9750-44 871	–	–	PHIS, Kelly et al,[32] Shander et al,[24] Abraham and Sun[25]
Manual or exchange	17 875	9750-26 000	–	–	
Apheresis	44 871	–	–	–	
Outpatient iron chelation	55 480	11 080-81 088	–	–	PHIS, Lexicomp[26]
Indirect costs					
Educational service	7402	5099-9705	8280	5704-10 855	Epping et al,[29] Chambers et al[28]

ED, emergency department; SD, standard deviation.

A simple cost-effectiveness analysis model was used to explore the preferred treatment of sickle cell anemia in children. Given that accurate health care costs are often difficult to obtain, we used a range of estimates for red blood cell transfusions and iron chelation therapy costs. In each of these scenarios, the costs of transfusion greatly exceeded any savings in hospitalization costs. Using deferoxamine instead of deferasirox in our sensitivity analyses significantly lowered the cost of transfusions to produce an incremental cost-effectiveness ratio as low as $4373. In the future, cheaper generic versions of deferasirox would change the incremental cost-effectiveness ratio as compared with standard care. We obtained costs for deferasirox from Canada ($24.89 per 500-mg tablet or $9080 yearly) as the potential cost of generic versions of deferasirox, which is significantly cheaper than the $55 480 from Lexicomp.[35] Also, the substitution of apheresis for exchange transfusion may eliminate the need for iron chelation therapy in some participants depending on a wide range of factors, including baseline hemoglobin level.[32] However, the procedure itself remained costly and would exceed the lowest potential cost of blood transfusions. Future strategies to decrease iron deposition and limit iron chelation costs include dose-escalated hydroxyurea and prolonging the time between regular blood transfusions and preliminary positive results.[36] Decreasing the costs of iron chelation will significantly affect costs for secondary prevention of infarct recurrence in children with preexisting cerebral infarcts.

The only available curative strategy for children with sickle cell anemia and strokes or silent strokes is hematopoietic stem cell transplantation, which has significant risks and great financial costs. Also, transplant costs can vary widely at different centers.[37,38] The number of years of accruing costs in other scenarios required to equal the transplant cost should be considered. Further research is needed to evaluate the cost-effectiveness of additional sickle cell anemia treatments for stroke prevention.

The incorporation of indirect costs allows for more complete comparisons of costs for interventions across different age groups. Extensive methods have been developed to assess indirect costs, which can generally be viewed as the potential losses or gains of output to the economy. Our analysis showed the saving of indirect costs from the societal perspective for preventing the incidence of new cerebral infarcts. However, if the full societal view was considered, we would need to incorporate elements including but not limited to avoided lost wages, supportive or residential care, benefits to psychosocial health of family members, and reduced costs associated with increased availability of time for family members due to reduced need for informal care. These additional direct and indirect cost-saving considerations for preventing cerebral infarct recurrence in students with sickle cell anemia would most likely enhance the economic favorability of regular blood transfusion. A more comprehensive assessment of the cost-effectiveness analysis from the society or the health care delivery view is needed.

As expected in the simple incremental cost-effectiveness analysis, our study has specific limitations. We elected to analyze individuals based on whether they received at least 6 months of blood transfusion. Thus, we may have underestimated the costs for the subgroup of participants that started regular blood transfusion therapy but did not continue for 36 months. The estimated costs were derived by using a formula based on the ratio of costs to charges and total hospital charges. Although this is a generally accepted method of comparing costs,[19] these costs may not be directly comparable to our estimates of the cost of blood products and iron chelation, which were derived from a combination of published literature and costs at a single institution. Another limitation is that we assumed that most outpatient costs were equivalent in the transfusion and standard care groups. A substantial difference in outpatient health care utilization could exist between the study groups but is unlikely a driver for increased cost-effectiveness. Sickle cell anemia adverse events such as priapism and avascular necrosis were lower in the transfusion group than in the standard care group. Specifically for priapism, the incidence rate ratio was 0.13 ($P = .02$) with an incidence rate of 0.8 and 6.65 events per 100 patient-years for

participations in the transfusion and standard care group, respectively. Similarly, for symptomatic avascular necrosis of the femoral head, the incidence rate ratio was 0.22 ($P = .02$), with an incidence rate of 0.49 and 2.25 events per 100 patient-years, respectively. A significantly lower incidence rate of priapism and symptomatic avascular necrosis would lead to high additional cost savings over time,[39-44] resulting in regular blood transfusions being more cost-effective if they were included in the analysis. Because we did not include these costs, our cost-effectiveness model for transfusion therapy is conservative.

As per the recent ASH guidelines for transfusion,[45] individuals who receive transfusions should receive minor red blood cell antigen matching; therefore, this red blood cell antigen matching practice is the standard of care. In the SIT Trial, the rate of alloantibodies was relatively low (red blood cell alloimmunization rate of 0.278 per 100 units of red blood cells). When red blood cell antigen testing was performed in concordance with ASH guidelines, delayed hemolytic transfusion reactions were not observed in the trial; if these reactions occurred, the costs of these events would add to the costs of transfusion.

In addition, study participants' use of hydroxyurea would be expected to significantly decrease hospitalization rates for the 2 most common causes, namely pain and ACS. However, recent data indicate that simply prescribing hydroxyurea does not translate into children with lower hospitalization rates. The vast majority of children with sickle cell anemia do not receive hydroxyurea.[46,47] Furthermore, the impact of lowering the incidence of cerebral infarct recurrence in sickle cell anemia on costs associated with other aspects of the lives of children with sickle cell anemia (eg, education) remained unanswered.

We calculated a simple incremental cost-effectiveness ratio and not in-depth decision modeling. Data from previously performed clinical trials that were not designed to evaluate cost-effectiveness, such as SIT, do not contain QALY data, and methods of QALYs of children are still being developed and validated.[48] Thus, we measured the effectiveness of critical clinical end points by using the prevention of neurologic events that cause significant morbidity. The cost per stroke avoided for primary stroke prevention with regular blood transfusions for elevated transcranial Doppler values in sickle cell anemia was £203 099 in a 2012 systematic review.[49] Based on inflation, the cost of primary stroke prevention was $323 105 in 2020.[50] Our incremental cost-effectiveness ratio was $22 025 per infarct recurrence prevented. This incremental cost-effectiveness ratio is significantly lower than that of a previous primary stroke prevention analysis.[49] Many reasons could account for these to different cost-effectiveness ratios, including different health care utilization assumptions. However, the 2 studies had a dramatic difference in the time horizon. Our cost-effectiveness analysis included only a 3-year time horizon vs the primary stroke prevention analysis, which included a lifetime time horizon. Our findings show the cost-effectiveness of regular blood transfusion for cerebral infarct recurrence. Future research establishing measurement of QALYs for children and adults with sickle cell anemia and cerebral infarct using an acceptable incremental cost-effectiveness ratio of $100 000 per QALY or $150 000 per QALY[51,52] can elucidate additional cost-effectiveness analysis to explore whether transfusions would be the preferred treatment.

Children with sickle cell anemia and silent cerebral infarcts receiving regular blood transfusions have a yearly 54% relative reduction in hospitalization cost compared with children with sickle cell anemia who do not undergo transfusion. However, this 54% reduction in hospitalization costs is only 5% to 28% of the estimated yearly costs for iron chelation and red blood cell transfusion. Although the potential savings of indirect costs for preventing a cerebral infarct with transfusion therapy was $2634 over our 3-year time horizon, this was less than the transfusion costs. The incremental cost-effectiveness ratio exhibits a reasonable cost of transfusions to prevent cerebral infarcts. Less expensive versions of deferasirox or strategies to minimize chelation therapy would significantly decrease transfusion costs. Efficacious strategies, other than regular blood transfusion therapy, for secondary stroke prevention in children with preexisting silent cerebral infarcts will reduce or eliminate iron chelation, significantly improving the cost-effectiveness of secondary stroke prevention.

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Authorship

Contribution: P.H., J.C.G., C.J.L., M.R.D., and R.M.C. designed the study; P.H., J.C.G., M.R.D., and R.M.C. collected the data; M.R., C.J.L., and R.M.C. performed the analyses; P.H., J.C.G., C.J.L., M.R.D., and R.M.C. interpreted the results; and P.H. and R.M.C. wrote the manuscript. Before submission, all authors reviewed and edited the manuscript.

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ORCID profiles: C.J.L., 0000-0001-9441-3508; M.R., 0000-0001-7258-0073; M.R.D., 0000-0002-0574-1604; R.M.C., 0000-0003-1916-6521.

Correspondence: Robert M. Cronin, Department of Internal Medicine, The Ohio State University, Graves Hall, 333 W 10th Ave, Columbus, OH 43210; e-mail: robert.cronin@osumc.edu.

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