

## RAPID COMMUNICATION

# A Modified Transfusion Program for Prevention of Stroke in Sickle Cell Disease

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Regular red blood cell transfusions reduce the rate of recurrent cerebral infarction in sickle cell disease but lead to accumulation of excessive iron. We studied the effect on the prevention of recurrent stroke and the volume of blood transfused of a modified transfusion program in which the pretransfusion percentage of hemoglobin S (HbS) was maintained at 50%, rather than the conventional 30%. Fifteen patients with sickle cell disease and cerebral infarction who had been free of recurrent stroke for at least 4 years during which the pretransfusion HbS was maintained below 30% were assigned to a transfusion program in which the HbS was allowed to increase to 50%. Transfusion regimens included simple transfusion and manual and automated partial exchange transfusion. The duration of follow-up was 14 to 130 months with a median duration of 84 months. None of the 15 patients had a recurrent cerebral infarction during 1,023 patient-months in which the target pretransfusion HbS was 50%. Analysis of this finding, using a binomial distribution, indicates that there is less than a 5% chance that the risk per patient of recurrent stroke in the first year of the

modified transfusion program is greater than 18%. One 23-year-old patient had a fatal intraventricular hemorrhage when the HbS was 30% and a 21-year-old patient had a fatal subarachnoid hemorrhage in the 40th week of pregnancy when the HbS was 29%. Blood requirements with simple transfusions decreased by 17% to 48% (mean 31%) when the target pretransfusion HbS level was increased from 30% to 50% ( $P < .001$ ). Manual or automated partial exchange transfusions and a target HbS level of 50% in eight patients reduced blood requirements by 33% to 99% (mean 67%) in comparison with simple transfusion and a target HbS level of 30% ( $P < .001$ ). This study offers evidence that a target pretransfusion HbS level of 50% affords a continuing high rate of protection against recurrent cerebral infarction in sickle cell disease after 4 years of a conventional transfusion program. Increasing the target HbS level from 30% to 50% provides a major reduction in blood requirements and lowers the rate of iron accumulation.

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**STROKE OCCURS** in approximately 6% to 10% of children with sickle cell disease and is usually associated with narrowing or occlusion of large cerebral arteries.<sup>1-3</sup> In the absence of transfusion therapy, approximately two thirds of patients who have had a stroke will suffer a recurrence,<sup>1,4,5</sup> usually within 2 years of the initial stroke.<sup>1</sup> Neurologic impairment after recurrent stroke may be particularly severe.<sup>1</sup>

The regular administration of red blood cell (RBC) transfusions dramatically reduces the risk of recurrent stroke.<sup>4,6</sup> The usual goal of the transfusion program is to reduce the hemoglobin S (HbS) level to less than 30% of the total hemoglobin. With such a program, the recurrence rate decreases to 0% to 10%. The optimal duration of transfusion therapy for prevention of recurrent stroke is unknown. When transfusions are stopped after 1 or 2 years, the recurrence rate is similar to that found in nontransfused patients.<sup>6</sup> Cessation of transfusion therapy even after 5 years is accompanied by an unacceptably high rate of recurrence.<sup>7</sup> The current practice in many centers is to continue transfusion therapy indefinitely.

A major complication of long-term transfusion therapy is iron overload.<sup>8</sup> Death due to cardiac failure or intractable arrhythmias usually occurs when the iron load exceeds 1 g per kilogram of body weight.<sup>9</sup> Few patients with sickle cell disease have been regularly transfused for 15 to 20 years, the duration associated with death from iron overload in transfusion-dependent disorders such as thalassemia major. However, studies of iron stores and organ function in patients with sickle cell disease who have received transfusions for 8 to 11 years suggest that these patients are susceptible to the same toxic effects of transfusional iron overload that occur in patients with thalassemia major.<sup>10</sup> To address the dual problems of recurrent stroke and transfusional iron overload in sickle cell disease, we have modified the conventional transfusion program by selecting a target level of HbS of 50% rather than 30%, and, for selected

patients, by replacing simple transfusion with manual or automated exchange transfusion. The aim of this study was to design a transfusion program that afforded protection against recurrent stroke similar to a conventional transfusion program, while reducing blood requirements and the rate of iron loading.

## MATERIALS AND METHODS

**Patients.** Fifteen patients with homozygous sickle cell disease and cerebral infarction at age 3 to 12 years were enrolled in the study at 10 to 21 years of age (mean 15 years, median 15 years). Details regarding the neurologic events and arteriographic findings in most of these patients have been reported previously.<sup>5</sup> Before enrollment in the modified transfusion protocol, all patients were free of clinical neurologic deterioration or clinical evidence of recurrent stroke for at least 4 years in which the HbS level was kept below 30%. All patients meeting these criteria were included.

Eleven patients received daily subcutaneous or intravenous infusions of the chelating agent deferoxamine for 2 to 11 years. Three patients refused chelation therapy and one patient died before beginning regular treatment with deferoxamine.

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**Transfusion protocol.** After a minimum of 4 years of simple RBC transfusion to maintain the HbS level below 30%, the target pretransfusion HbS level was increased to 50%. The requirement of 4 years of conventional transfusion therapy was selected because most recurrent strokes in transfused or nontransfused patients have occurred during this time. For patients who continued to receive simple transfusions, the HbS level was increased to 50% by decreasing the amount of blood transfused or by increasing the interval between transfusions. For patients who moved directly to partial exchange transfusion, the HbS level was increased to 50% by adjusting the proportions of blood removed from the patient and donor blood administered to the patient (see below). Washed, frozen-thawed, or leukocyte-poor donor RBCs were used for all transfusions.

Manual partial exchange transfusions were performed by removing 500 mL of blood from the patient and administering 250 mL of donor RBCs and 250 mL of normal saline. This procedure was repeated one or two times as needed to maintain the pretransfusion HbS level below 50%. One unit of RBCs was administered at the end of the partial exchange transfusion if the previous HbS level was greater than 55% to 60%. Automated exchange transfusion was performed using the Haemonetics V50 Blood Cell Processor (Haemonetics Corp, Braintree, MA). In this procedure, blood totaling approximately 600 to 1,200 mL with an average hematocrit of 50% was removed with return of 2 or 3 U of donor RBCs; the patient's RBCs were discarded and the plasma was returned along with a small amount of supplemental normal saline.<sup>11</sup>

The percentages of HbS and HbA were determined before each transfusion by densitometric analysis of hemoglobin bands after separation by electrophoresis at pH 8.6 on cellulose acetate. If the pretransfusion HbS level decreased below 40% or increased above 60%, the interval between transfusions was altered or the amount of blood administered was modified to return the HbS to the appropriate level.

**Measurement of blood requirements.** Annual blood requirements were expressed as milliliters of packed RBCs per kilogram of body weight at mid-year (mL RBC/kg/yr). For simple transfusions, the volume of each unit was measured and used to calculate the annual blood requirements. The hematocrits of these units were measured intermittently and varied little from the average value of 75%. For exchange transfusion, the volume of blood was calculated as the net gain of blood at a hematocrit of 75%, so that annual blood requirements with simple and exchange transfusion could be compared directly. Blood requirements for the first 6 months after changing the target HbS level from 30% to 50% were excluded from the analysis.

Two of 15 patients were excluded from the analysis of transfusion requirements but included in the analysis of recurrent stroke at the higher HbS level. One of the two patients received several transfusions at another institution where the volume and hematocrit of the administered blood were not measured. The other patient had a chronic autoimmune hemolytic anemia, and his blood requirements varied in relationship to the severity of the immune process.

**Informed consent.** The study was approved by the Committee for Protection of Human Subjects of the Children's Hospital of Philadelphia. Informed consent was obtained from patients and/or parents at the time of enrollment.

**Statistical analysis.** To obtain the largest probability of stroke per patient for which the probability of obtaining the observed number of strokes or less is 5%, in a sample size of 15, we used a binomial distribution. Blood requirements with conventional and modified transfusion regimens were compared using the Student's *t*-test for paired samples.

## RESULTS

**Recurrence of cerebral infarction during transfusion therapy.** The HbS level of the 15 subjects enrolled in the study was maintained below 30% for a total of 1,184 patient-months before modification of the transfusion protocol (Table 1). The range for individual patients was 48 to 121 months (mean 79 months, median 83 months). During this period, no patient had a recurrent stroke, fulfilling the eligibility requirement for increasing the HbS level to 50%. During 1,023 patient-months (individual range 14 to 130 months, mean 68 months, median 84 months) in which the target HbS level was 50%, no patient had a recurrent cerebral infarction. Twelve of the 15 patients have maintained a pretransfusion target HbS level of 50% for 2 or more years and eight patients have maintained this level for 7 or more years.

Using the binomial distribution, we calculated the greatest probability of stroke per patient for which the chance of observing zero strokes in 15 patients was 5%. There is less than a 5% chance that we would have observed no strokes with the modified transfusion program if the probability of stroke per patient were 18% or higher. A similar analysis of the 12 patients enrolled in the modified transfusion program for more than 2 years demonstrates that there is less than a 5% chance that we would have observed no strokes if the probability of stroke per patient were 22% or higher.

**Other neurologic events.** Neurologic complications other than cerebral infarction occurred in two patients during the modified transfusion program. One patient suffered an intraventricular hemorrhage and died at the age of 23 years. He had received regular RBC transfusions for 10 years. The HbS level was kept below 30% during the first 7 years and below 50% during the next 3 years. His HbS level was 30% at the time of the hemorrhage, which occurred 1 day after his last transfusion. A computed tomography (CT) scan showed massive intraventricular hemorrhage and an old frontal infarct.

A second patient suffered a fatal intracranial hemorrhage in the 40th week of pregnancy. She was 21 years old and had been transfused for 9 years, including 4 years in which the HbS was kept below 30% and 5 years in which the HbS was kept below 50%. Her HbS level was 29% at the time of the bleed. A CT scan showed massive subarachnoid hemorrhage but no new infarct.

Another patient remained free of recurrent stroke during 9 years of transfusion therapy, including 5 years at an HbS below 30% and 4 years at an HbS below 50%. Three months after cessation of transfusion therapy she had a recurrent cerebral infarction. No HbA was present on hemoglobin electrophoresis. Transfusion therapy was reinstated and she had no further strokes during the next 48

**Table 1. Effect of Modified Transfusion Program on Recurrence of Cerebral Infarction**

Target Pretransfusion HbS Level (%)	Patient-Months	Recurrent Cerebral Infarction
30	1,184	0
50	1,023	0

months in which her HbS was kept below 50%. The higher HbS level was chosen because of noncompliance with iron chelation therapy. She subsequently died of complications related to transfusional iron overload.

**Transfusion requirements.** Transfusion requirements were evaluated in 13 patients. Nine patients continued to receive simple transfusions as the HbS level was increased from 30% to 50%. Transfusion requirements in the final year at an HbS level below 30% (mean HbS 22%, range 15% to 33%) were 120 to 188 mL packed RBC/kg/yr (mean 147 mL/kg/yr) (Fig 1). After the target HbS level was increased to 50%, the patients required 83 to 123 mL/kg/yr (mean 100 mL/kg/yr) to maintain an actual HbS level of 41% to 53% (mean 45%). The increase in the target HbS level was accompanied by a decrease in transfusion requirements of 17% to 48% (mean 31%). The difference in blood requirements when the target HbS level was changed from 30% to 50% was significant at  $P < .001$ .

Manual or automated exchange transfusion was used to maintain the HbS level below 50% in eight patients. In four cases, institution of exchange transfusion began at the same time the target HbS level was increased to 50%, while in four cases exchange transfusion replaced simple transfusion after the target HbS level was increased to 50%. The net blood requirements with manual exchange transfusion in three patients were 44 to 90 mL/kg/yr (mean 60 mL/kg/yr) to maintain an HbS level of 40% to 42% (mean 41%) (Fig 2). Net blood requirements with automated exchange transfusion in five patients were 2 to 96 mL/kg/yr (mean 41 mL/kg/yr) to maintain an HbS level of 36% to 56% (mean 46%). The decrease in blood requirements when the HbS was increased from 30% to 50% and exchange transfusion (manual or automated) used in place of simple transfusion was 33% to 99% (mean 67%); the difference in individual blood requirements was significant at  $P < .001$ .

DISCUSSION

Stroke in children with sickle cell disease has presented a difficult therapeutic challenge. In the absence of a safe and accurate method for identifying individuals at risk for an

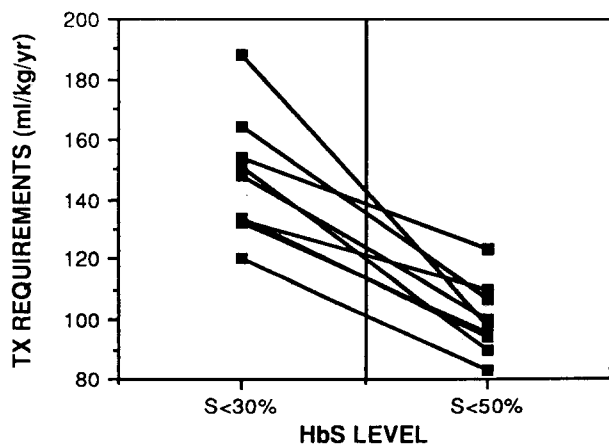


Fig 1. Blood requirements with simple transfusion before and after increasing the pretransfusion HbS level from 30% to 50%.

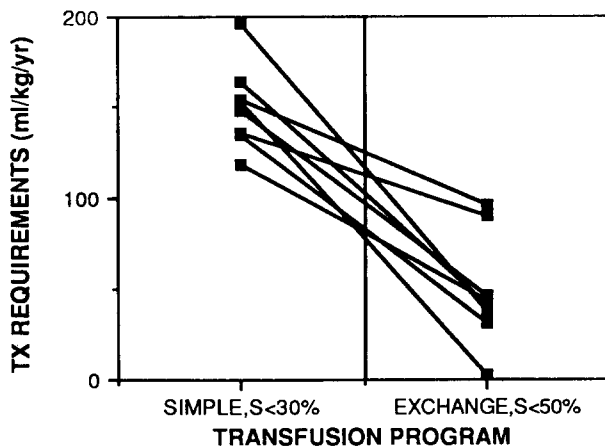


Fig 2. Comparison of transfusion requirements using simple transfusion to maintain the pretransfusion HbS below 30% and using manual or automated partial exchange transfusion to maintain the HbS level below 50%.

initial stroke, attention has been focused on prevention of recurrent stroke. Several studies have demonstrated that regular transfusion of RBCs sharply reduces the rate of recurrent stroke.<sup>4-6</sup> In these studies as well as in most clinical practice, the transfusion program is designed to reduce the HbS level to less than 30% of the total hemoglobin by adding RBCs containing normal hemoglobin to suppress the patient's endogenous erythropoiesis (simple transfusion) or by replacing the patient's RBCs with normal donor cells (exchange transfusion). The rationale for the choice of an HbS level of 30% is not clear, although studies of viscosity in vitro have shown favorable conditions of flow when the HbS is reduced below 40% of total hemoglobin by the addition of cells containing normal hemoglobin.<sup>12,13</sup>

The appropriate duration of transfusion therapy for prevention of recurrent stroke is uncertain. In a previous study, investigators stopped transfusions after 1 or 2 years in 10 subjects; seven had a new stroke within 5 weeks to 11 months.<sup>6</sup> Recently, the same group of investigators found a persistently high rate of recurrent stroke when transfusion therapy was stopped after 5 to 12 years.<sup>7</sup> These studies indicate that lifelong transfusion therapy may be necessary to prevent recurrent stroke in many patients with sickle cell disease.

The results of the present study suggest that the use of a target HbS level of 50% rather than 30% may provide continuing protection against recurrent stroke in comparison with cessation of transfusion. However, even though no cerebral infarctions occurred during 1,023 patient-months with the modified transfusion program, the sample size is too small to conclude that a target HbS level of 50% is equally effective as 30% in preventing recurrent stroke. With 95% probability, the probability of recurrent stroke per patient in the first year of the modified transfusion program is less than 20%. In light of the clinical advantages of reducing blood requirements, these results provide a strong justification for an expanded study of the modified transfusion program.

Two patients in this study suffered hemorrhages at the ages of 21 and 23 years. This complication of sickle cell disease is rare in children but more common in adults.<sup>1</sup> Both patients had received RBC transfusions for many years. Although the target pretransfusion HbS level had been increased to 50% 3 and 4 years earlier, measured HbS levels at the time of the bleeding episodes were 30% and 29%. Recent evidence suggests that children with cerebral infarctions are at increased risk of later intracranial hemorrhage even when treated with long-term transfusion for prevention of recurrent stroke.<sup>14</sup>

Patients were selected for this study if they were free of clinical neurologic deterioration or clinical evidence of recurrent stroke for at least 4 years with a conventional transfusion program to maintain the HbS level below 30%. In our center and elsewhere, a few patients have had recurrent transient ischemic attacks and strokes when the HbS was less than 30%.<sup>5,6,15</sup> These individuals may have unusually severe arterial abnormalities so that relatively small amounts of circulating cells containing HbS are sufficient to cause impaired cerebral blood flow. Alternatively, factors other than circulating sickle cells may be responsible for stroke. The uncommon recurrences in transfused patients usually happen within 4 years of the initial stroke.<sup>15</sup> A 4-year period of transfusion therapy to reduce the HbS level to below 30% should identify most of these particularly susceptible patients before the intensity of transfusion therapy is decreased. However, it is likely that a few patients will have late recurrences of stroke at an HbS of 50% just as other patients have had late recurrences at an HbS less than 30%. In addition, it is possible that subtle neuropsychological abnormalities may occur during a long-term transfusion program, even in the absence of recurrent stroke.

Long-term transfusion therapy in the treatment of other hemoglobinopathies such as thalassemia major leads to the steady accumulation of excessive iron and, in the absence of chelation therapy, death due to iron-induced organ failure.<sup>16</sup> Patients with sickle cell disease who receive regular RBC transfusions for prevention of recurrent stroke develop markedly increased iron stores and findings of liver and cardiac dysfunction that are typical of iron overload.<sup>10,17</sup> Chelation therapy with deferoxamine increases iron excretion and reduces excessive iron stores in patients with sickle cell disease but poses the same problems of discomfort, cost, compliance, and long-term safety that are well de-

scribed in thalassemia.<sup>18,19</sup> Reduction of the rate of iron loading by modifying the transfusion program for prevention of recurrent stroke would increase the effect of chelation therapy on iron balance or perhaps remove the need for chelation therapy altogether. In the present study, four of the patients receiving automated RBC exchange to keep the HbS below 50% currently maintain ferritin levels below 500  $\mu\text{g/L}$  without further chelation therapy. For simple transfusion, the overall impact of the change in the target level of HbS on body iron stores is difficult to assess because of the additional influence of changes in chelation therapy that have accompanied the modification of transfusion therapy.

A change in the target HbS level from 30% to 50% lowers blood requirements and therefore decreases the rate of iron loading. Lowering the intensity of a simple transfusion program alone decreases blood requirements by an average of 31%. Use of manual or automated partial exchange transfusion to maintain the HbS level below 50% further reduces blood requirements so that annual transfusion needs decrease by an average of 67% in comparison with simple transfusion to maintain the HbS below 30%. The annual blood requirements to maintain the HbS below 50% with automated RBC exchange in patients with sickle cell disease are approximately 25% of those in a typical simple transfusion program for splenectomized patients with thalassemia major,<sup>20</sup> suggesting that the former method will markedly delay the accumulation of toxic amounts of iron.

Future studies using techniques such as transcranial Doppler or magnetic resonance angiography may identify children with sickle cell disease and stroke who do not require transfusion therapy or who can stop transfusion therapy safely after a limited time. Other studies may identify safe and effective methods for preventing sickling, as, for example, by increasing the amount of fetal hemoglobin or by allogeneic bone marrow transplantation.<sup>21,22</sup> In the meantime, most children with sickle cell disease and stroke receive long-term RBC transfusions. For selected patients, reducing the intensity of transfusion therapy after 4 years offers continued protection against recurrent cerebral infarction and reduces the likelihood of severe organ damage or death due to iron overload.

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#### REFERENCES

1. Powars D, Wilson B, Imbus C, Pegelow C, Allen J: The natural history of stroke in sickle cell disease. *Am J Med* 65:461, 1978
2. Sarnaik SA, Lusher JM: Neurological complications of sickle cell anemia. *Am J Pediatr Hematol Oncol* 4:386, 1982
3. Stockman JA, Nigro MA, Mishkin MM, Oski FA: Occlusion of large cerebral vessels in sickle cell anemia. *N Engl J Med* 87:846, 1972
4. Sarnaik S, Soorya D, Kim J, Ravindranath Y, Lusher J: Periodic transfusions for sickle cell anemia and CNS infarction. *Am J Dis Child* 133:1254, 1979
5. Russell MO, Goldberg HI, Hodson A, Kim HC, Halus J, Reivich M, Schwartz E: Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. *Blood* 63:162, 1984
6. Wilimas J, Goff JR, Anderson HR Jr, Langston JW, Thompson E: Efficacy of transfusion therapy for one to two years in patients with sickle cell disease and cerebrovascular accidents. *J Pediatr* 96:205, 1980
7. Wang WC, Kovnar EH, Tonkin IL, Mulhern RK, Langston JW, Day SW, Schell MJ, Wilimas JA: High risk of recurrent stroke

after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *J Pediatr* 118:377, 1991

8. Jacobs A: Iron overload-clinical and pathologic aspects. *Semin Hematol* 14:89, 1977

9. Modell, Berdoukas V: *The Clinical Approach to Thalassemia*. London, UK, Grune & Stratton, 1984, p 163

10. Cohen A, Kron E, Brittenham G: Toxicity of transfusional iron overload in sickle cell anemia. *Blood* 64:47a, 1984 (abstr, suppl)

11. Kim HC, Barrett MS, Preisendanz H: Modified erythrocytapheresis to retard transfusion-induced iron overload in chronically transfused sickle cell patients. *Transfusion* 28:24S, 1988 (abstr)

12. Murphy JR, Wengard M, Brereton W: Rheological studies of HbSS blood: Influence of hematocrit, hyperviscosity, separation of cells, deoxygenation, and mixture with normal cells. *J Lab Clin Med* 87:475, 1976

13. Lessin LS, Kurantsin-Mills J, Klug PP, Weems HB: Determination of rheologically optimal mixtures of AA and SS erythrocytes. *Blood* 50:111, 1977 (abstr, suppl)

14. Powars D, Adams RJ, Nichols FT, Milner P, Charache S, Sarnaik S: Delayed intracranial hemorrhage following cerebral infarction in sickle cell anemia. *J Assoc Acad Minority Phys* 1:79, 1990

15. Buchanan GR, Bowman WP, Smith SJ: Recurrent cerebral ischemia during hypertransfusion therapy in sickle cell anemia. *J Pediatr* 103:921, 1983

16. Cohen A: Management of iron overload in the pediatric patient. *Hematol Oncol Clin North Am* 1:521, 1987

17. Buja LM, Roberts C: Iron in the heart. *Am J Med* 51:209, 1971

18. Cohen A, Schwartz E: Excretion of iron in response to deferoxamine in sickle cell anemia. *J Pediatr* 92:659, 1978

19. Cohen A, Schwartz E: Iron chelation therapy in sickle cell anemia. *Am J Hematol* 7:69, 1979

20. Cohen A, Markenson AL, Schwartz E: Transfusion requirements and splenectomy in thalassemia major. *J Pediatr* 97:100, 1980

21. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, Nathan DG: Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. *J Clin Invest* 74:652, 1984

22. Vermeylen C, Ninang J, Fernandez-Robles E, Cornu G: Bone marrow transplantation in five children with sickle cell anaemia. *Lancet* 1:1427, 1988