ABSTRACT

Background  Blood transfusions prevent recurrent stroke in children with sickle cell anemia, but the value of transfusions in preventing a first stroke is unknown. We used transcranial Doppler ultrasonography to identify children with sickle cell anemia who were at high risk for stroke and then randomly assigned them to receive standard care or transfusions to prevent a first stroke.

Methods  To enter the study, children with sickle cell anemia and no history of stroke had to have undergone two transcranial Doppler studies that showed that the time-averaged mean blood-flow velocity in the internal carotid or middle cerebral artery was 200 cm per second or higher. The patients were randomly assigned to receive standard care or transfusions to reduce the hemoglobin S concentration to less than 30 percent of the total hemoglobin concentration. The incidence of stroke (cerebral infarction or intracranial hemorrhage) was compared between the two groups.

Results  A total of 130 children (mean [±SD] age, 8.3±3.3 years) were enrolled; 63 were randomly assigned to receive transfusions, and 67 to receive standard care. At base line, the transfusion group had a slightly lower mean hemoglobin concentration (7.2 vs. 7.6 g per deciliter, P=0.001) and hematocrit (20.4 vs. 21.7 percent, P=0.002). Ten patients dropped out of the transfusion group, and two patients crossed over from the standard-care group to the transfusion group. There were 10 cerebral infarctions and 1 intracerebral hematoma in the standard-care group, as compared with 1 infarction in the transfusion group—a 92 percent difference in the risk of stroke (P<0.001). This result led to the early termination of the trial.

Conclusions  Transfusion greatly reduces the risk of a first stroke in children with sickle cell anemia who have abnormal results on transcranial Doppler ultrasonography.

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PREVENTION OF A FIRST STROKE BY TRANSFUSIONS IN CHILDREN WITH SICKLE CELL ANEMIA AND ABNORMAL RESULTS ON TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

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STROKE occurs by the age of 20 in about 11 percent of patients with sickle cell anemia.1,3 The most frequent cause of brain infarction in these patients is blockage of the intracranial internal carotid and middle cerebral arteries.4,5 These lesions can be detected by transcranial Doppler ultrasonography6,7 because blood-flow velocity is inversely related to arterial diameter. High blood-flow velocity has been correlated with stenosis on angiography,7 increased cerebral blood flow,8 and subsequent stroke in children with sickle cell anemia.9,10 In a cohort of 315 children9,10 with no history of stroke, the risk of a stroke increased significantly with increasing velocity of blood flow in the internal carotid artery or middle cerebral artery. This finding is the basis of our primary stroke-prevention trial in children with sickle cell anemia. Blood transfusion was used because it is highly effective in reducing the risk of recurrent stroke in sickle cell anemia.11,12 The Stroke Prevention Trial in Sickle Cell Anemia tested the hypothesis that periodic blood transfusion, with reduction of the hemoglobin S concentration to less than 30 percent of the total hemoglobin concentration, would lower the risk of stroke by 70 percent as compared with the risk associated with standard care.13
METHODS

Subjects

Patients who were 2 to 16 years of age and who had been given a diagnosis of sickle cell anemia or sickle β-thalassemia were eligible for screening by transcranial Doppler ultrasonography. Patients were excluded from the study if they had a history of stroke, had an indication for or contraindication to long-term transfusion, were receiving other treatments that affected the risk of stroke, were infected with the human immunodeficiency virus (HIV), or were pregnant. Informed consent was obtained from the parents’ patients or guardians.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonographers were trained to follow a protocol similar to that used in adults,5 but modified for children with sickle cell anemia.12–14 Examiners used identical equipment (2-MHz pulsed Doppler ultrasonograph, model EME TC 2000, Nicolet, Madison, Wis.) and recorded the highest time-averaged mean blood-flow velocity in 2-mm increments in the middle cerebral artery (at three points), the distal internal carotid artery, the anterior and posterior cerebral arteries, and the basilar artery. Experts at the Medical College of Georgia who were unaware of the patients’ conditions read the results and categorized them as normal, conditional, abnormal, or inadequate. If all velocities were less than 170 cm per second, the results were considered to be normal. A velocity of at least 170 but less than 200 cm per second was considered to be conditional. To be considered abnormal, blood-flow velocity had to be at least 200 cm per second in either the internal carotid artery or the middle cerebral artery. To enter the study, each patient had to have abnormal results on two transcranial Doppler studies. The use of a permuted block design approximately balanced treatment assignment within centers. The cutoff point was taken from pilot studies13,14 in which a flow rate of 200 cm per second was associated with a 40 percent risk of stroke within three years.

Treatment Protocol

The base-line evaluation included magnetic resonance imaging (MRI)12, a structured neurologic examination; a physical examination; medical history taking; a complete blood count with differential, platelet, and reticulocyte counts; quantitative hemoglobin analysis by high-performance liquid chromatography13, determination of the sickle-cell gene haplotype; mapping of the α-globin gene; liver-function tests (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, lactate dehydrogenase, and bilirubin); serum ferritin measurement; and assessment for prior infection with hepatitis B and C viruses.

Concomitant care included penicillin prophylaxis, pneumococcal vaccination, folic acid supplementation, surgery, and treatment of acute illness, including the use of transfusion when needed for transient episodes but excluding the use of hydroxyurea or antisickling agents. Vaccination against hepatitis B was required if appropriate.

Patients were randomly assigned to receive either standard care or transfusions. The goal in using transfusions was to reach the target hemoglobin S concentration (<30 percent of total hemoglobin) within a period of 21 days without exceeding a hemoglobin concentration of 12 g per deciliter and a hematocrit of 36 percent, measured before transfusion. Exchange or simple transfusions were allowed. Red cells that were negative for hemoglobin S and depleted of leukocytes were delivered in a volume of approximately 10 to 15 ml per kilogram of packed cells per transfusion. The concentration of hemoglobin S was determined by high-performance liquid chromatography at the Medical College of Georgia.13 Blood was matched for the ABO blood group, the Kell (K) blood group, and Rh antigens C, D, and E.

Once their hemoglobin S concentration was 30 percent of total hemoglobin or less, children received transfusions every three to four weeks. Adverse reactions to transfusion including hemolytic, allergic, and febrile reactions; anaphylaxis; circulatory overload; hypertension; and hemoglobinuria and alloimmunization were recorded. The complete blood count, platelet and reticulocyte counts, and measurements of hemoglobin S, ferritin, and liver enzymes were performed quarterly. Tests for antibodies to HIV, human T-cell lymphotropic virus type I (HTLV-I), hepatitis B surface antigen, and hepatitis C were performed at base line and at the end of the study.

End Points

The protocol was intended to identify all neurologic events. A panel of physicians with no knowledge of the children’s treatment assignments who were not affiliated with the study centers determined whether an event was a stroke. The primary end points were cerebral infarction and intracranial hemorrhage. Focal symptoms consistent with the occurrence of a cerebral infarction or an intracerebral hematoma were required unless the presentation suggested a diagnosis of subarachnoid hemorrhage. MRI studies obtained after the events were compared with those obtained at base line and annually thereafter. In the absence of supporting MRI findings, clear and compelling clinical evidence of a stroke was required. Transient symptoms were included if changes consistent with the occurrence of stroke were evident on MRI.

Statistical Analysis

Base-line characteristics including age; sex; concentrations of hemoglobin S, fetal hemoglobin, and total hemoglobin; blood-flow velocity on the confirmatory transcranial Doppler study (the second of two qualifying examinations with abnormal results); and the presence or absence of ischemic lesions at base line on MRI were compared by the t-test or chi-square test. The incidence of stroke was compared between the groups with an unadjusted proportional-hazards regression model10 according to the intention to treat. The severity of stroke was estimated at hospital discharge with the modified Rankin scale.12 Four interim analyses and one final analysis were planned, with the Lan–DeMets approximation of the O’Brien–Fleming stopping boundary.13 The date of the first analysis was changed from 20 months to 14 months after recruitment began.

The data and safety monitoring board was appointed by the National Heart, Lung, and Blood Institute to approve the protocol and consent procedures, oversee data collection and patient safety, and recommend discontinuation of the trial if serious safety or ethical issues arose. The board consisted of two pediatric hematologists, a pediatric neurologist, two statisticians, two neuroradiologists, and one medical ethicist.

RESULTS

Screening began in January 1995 and ended in November 1996 after 3929 transcranial Doppler studies had been performed on 1934 children. The base-line rate of abnormal results for all children was 9.7 percent and was higher among children 2 to 8 years of age (120 of 1117, or 10.7 percent) and 9 to 12 years of age (47 of 502, or 9.4 percent) than among those who were 13 to 16 years of age (20 of 315, or 6.3 percent) (P=0.03 by the Mantel–Haenszel test for trend). Seventy-nine children who had normal results at the first screening subsequently had abnormal results. Of 266 children with abnormal results on one Doppler study, 242 had at least one subsequent examination, the results of which were also abnormal in the cases of 206 children (85 percent). Of these 206 patients, who were eligible for the study because they had abnormal re-
sults on two Doppler examinations, 14 were found to be ineligible for other reasons: 5 had high serum ferritin concentrations, 4 declined to undergo HIV testing, 1 had a stroke before randomization, 1 was unable to start treatment, 1 had a contraindication to transfusion, and in the case of 2 others an indication for transfusion developed after the Doppler studies. Sixty-two patients declined to undergo randomization or were not enrolled by the investigators: 35 expressed reluctance to receive transfusions (34 children) or standard care (1); 17 were not enrolled because of investigators’ concern about compliance, and 10 others did not give a reason for refusing to participate. The patients who were not enrolled did not differ substantially from those who were enrolled in terms of age, sex, blood-flow velocity, or hematologic characteristics.

We enrolled 130 children (60 boys and 70 girls), including five pairs of siblings, in the study: 63 were randomly assigned to receive transfusions, and 67 to standard care. The status of all but one child was known when the trial was halted in September 1997. One patient with a serum ferritin concentration of more than 500 ng per milliliter was approved for entry because a liver biopsy showed low iron stores. Base-line hemoglobin and hematocrit values were slightly lower in the transfusion group (Table 1). The blood-flow velocity recorded during the confirmatory transcranial Doppler study and the prevalence of abnormalities on MRI did not differ significantly between the two groups.

Ten patients dropped out of the transfusion group at the outset or after 2 to 23 months. One patient had multiple alloantibodies, one was found to be ineligible because the results of only one Doppler study were abnormal (the results of the other were conditional), four had problems with compliance, and four dropped out for unspecified reasons. One of these 10 patients was subsequently lost to follow-up. Two patients crossed over from the standard-care group to the transfusion group, one on day 2 because the base-line MRI showed a subacute intracerebral hematoma. MRI findings and the patient’s history of headache 31 days before the test suggested that the hematoma had occurred before randomization, but the event was counted as occurring on day 2. The other patient started receiving transfusions after 12 months because of leg ulcers.

The 63 patients in the transfusion group received a total of 1521 transfusions. Most were simple trans-
fusions (63 percent), 12 percent were exchange transfusions, and 25 percent were a combination of simple and exchange transfusions. The mean (±SD) serum ferritin concentration in the transfusion group increased from 164±155 ng per milliliter at base line to 1804±773 ng per milliliter at 12 months (range, 945 to 5773 in 51 patients) and 2509±974 ng per milliliter at 24 months (range, 912 to 5702 in 23 patients). In 10 patients evidence of alloimmunization against red-cell antigens developed; 4 had antibodies to E or K antigens, and 6 to other red-cell antigens. There were 16 mild reactions to blood products or transfusion procedures in 12 patients. In no patient did evidence of hepatitis C infection develop, and all 100 children who were tested were negative for antibodies against HIV and HTLV-I. Central venous catheters were implanted in five children.

The mean interval between transfusions was 25±8 days. After the exclusion of the first 28 days after randomization, we found that 46 patients (78 percent of those who received transfusions) had at least one hemoglobin S measurement that exceeded 30 percent of the total hemoglobin concentration. The 143 episodes in which the target was exceeded were usually isolated and minor: in 70 cases (49 percent) values were in the range of 30.0 to 34.9 percent, in 31 cases (22 percent) values were in the range of 35.0 to 39.9 percent, and in 42 cases (29 percent) values were 40.0 percent or higher.

Twenty-nine potential strokes were assessed in 23 patients. Eleven children in the standard-care group and one child in the transfusion group had a stroke (Table 2). None of the patients who crossed over either to or from the transfusion group had a stroke. There were no deaths. Ten of these strokes were reported at the time symptoms occurred, and one was discovered at a quarterly visit. One of the strokes was an intracerebral hematoma and was discovered on the base-line MRI. When the child with the intracerebral hematoma was included in the primary analysis, the difference between treatments was significant (P<0.001), with the risk of stroke being 92 percent lower in the transfusion group. When this patient was excluded from the analysis (Fig. 1), the risk of stroke in the transfusion group was still 91 percent lower (P=0.002). In the standard-care group the rate of stroke was 10 percent per year. The single stroke in the transfusion group occurred after 26 months. The stroke-free survival curve in the transfusion group in Figure 1 shows a relatively large drop (from 100 percent to 92 percent) because only 13 patients had been followed for 26 months when the study was halted. Because of the high rate of stroke in the standard-care group and the significant effect of transfusion found at the second interim analysis, the data safety and monitoring board recommended that the trial be stopped 16 months before the planned date of December 1998 so that transfusion could be offered to children in the standard-care group.

The 11 patients with cerebral infarction presented with hemiparesis, but weakness had resolved by the time of the neurologic examination. Of these 11 patients, 10 were hospitalized. At discharge, two had major disability, five had mild-to-moderate disability, two had symptoms but no disability, and one was asymptomatic. All infarctions were in the carotid circulation, and MRI showed new or larger lesions in the symptomatic hemisphere in all but one patient.

### Table 2. Length of Follow-up and Number of Primary Events.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TOTAL (N=130)</th>
<th>TRANSFUSION (N=63)</th>
<th>STANDARD CARE (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (mo)</td>
<td>2550</td>
<td>1321</td>
<td>1229</td>
</tr>
<tr>
<td>Median</td>
<td>21.1</td>
<td>22.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>19.6±6.5</td>
<td>21.0±5.7</td>
<td>18.3±7.0</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>12</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>11</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 1.** Kaplan–Meier Estimate of the Probability of Not Having a Stroke among Patients Receiving Long-Term Transfusion and Patients Receiving Standard Care.

The P value was calculated by proportional-hazards regression analysis. Tick marks indicate the lengths of observation of patients who did not have a stroke. One patient in the standard-care group who had an intracerebral hematoma was excluded from the analysis.
PREVENTION OF A FIRST STROKE BY TRANSFUSIONS IN CHILDREN WITH SICKLE CELL ANEMIA

Table 3. Characteristics of the 11 Patients Who Had Cerebral Infarctions.*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Entry (yr)</th>
<th>Hb S/Fetal Hb at Entry (%)</th>
<th>Blood-Flow Velocity† (cm/sec)</th>
<th>Base-Line MRI Lesions‡</th>
<th>Time from Study Entry to Stroke (mo)</th>
<th>Symptoms</th>
<th>Post-Stroke MRI Lesions</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>96/2</td>
<td>251/257</td>
<td>Yes/Yes</td>
<td>14</td>
<td>Left hemiparesis, dysarthria</td>
<td>Yes (worse)</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>78/21</td>
<td>216/229</td>
<td>No/No</td>
<td>24</td>
<td>Right hemiparesis, aphasia</td>
<td>No</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>82/16</td>
<td>148/201</td>
<td>Yes/Yes</td>
<td>4</td>
<td>Right hemiparesis, seizure</td>
<td>Yes</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>92/6</td>
<td>202/204</td>
<td>Yes/Yes</td>
<td>21</td>
<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>94/3</td>
<td>246/264</td>
<td>Yes/Yes</td>
<td>1</td>
<td>Left hemiparesis, dysarthria</td>
<td>Yes (new)</td>
<td>Yes (new)</td>
<td></td>
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<tr>
<td>6</td>
<td>8</td>
<td>81/16</td>
<td>170/244</td>
<td>Yes/No</td>
<td>14</td>
<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
<td>Yes (new)</td>
<td></td>
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<tr>
<td>7</td>
<td>7</td>
<td>89/9</td>
<td>287/189</td>
<td>No/No</td>
<td>15</td>
<td>Left hemiparesis, dysarthria</td>
<td>Yes (new)</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>91/7</td>
<td>219/319</td>
<td>Yes/No</td>
<td>4</td>
<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>89/8</td>
<td>217/201</td>
<td>Yes/Yes</td>
<td>18</td>
<td>Left hemiparesis, dysarthria</td>
<td>Yes (worse)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>91/6</td>
<td>203/186</td>
<td>No/No</td>
<td>9</td>
<td>Left hemiparesis</td>
<td>Yes (new)</td>
<td>Yes (new)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>76/3§</td>
<td>225/156</td>
<td>No/No</td>
<td>26</td>
<td>Left hemiparesis, dysarthria, facial weakness</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*One patient with left frontal hemorrhage at base line was excluded. Hb denotes hemoglobin, and MRI magnetic resonance imaging.
†Values are the highest time-averaged mean velocity recorded in the middle cerebral artery or internal carotid artery during the confirmatory Doppler study.
‡Signs of atrophy were excluded.
§Patient 11, who was assigned to the transfusion group, had received a transfusion 11/2 weeks before entering the study.

(Table 3). Base-line results of transcranial Doppler studies were abnormal on the side on which the stroke occurred, but the results were also abnormal on the opposite side in six patients. Of seven patients with abnormalities on base-line MRI, two subsequently had a stroke in the hemisphere opposite to the base-line lesion.

We attempted to determine whether considering the results of the base-line MRI and hemoglobin and hematocrit measurements added to the ability of transcranial Doppler studies to predict stroke. For this purpose we analyzed the standard-care group, excluding the patient with hematoma. The analysis was confounded by a correlation between results of the MRI and Doppler studies. Patients with a blood-flow velocity of 240 cm per second or higher were more likely to have MRI lesions than patients with velocities of 200 to 239 cm per second (9 of 15 patients, or 60 percent, vs. 16 of 51 patients, or 31 percent; P=0.045 by the chi-square test). Proportional-hazards regression showed that the results of transcranial Doppler and MRI studies were significant predictors of stroke when considered separately (P=0.010 and P=0.038, respectively), but hemoglobin (P=0.12) and hematocrit (P=0.12) values were not. Only the transcranial Doppler study was significant when both MRI and Doppler studies were considered together (P=0.08 and P=0.03, respectively).

DISCUSSION

The current trial was made possible by the availability of transcranial Doppler ultrasonography, which is a safe and relatively inexpensive technique with reproducible results. The high rate of stroke in children with abnormal results on transcranial Doppler studies and the marked efficacy of transfusion support the clinical application of the strategy we used. The two randomized groups in this trial were balanced, except for base-line hemoglobin and hematocrit values. If this small difference had any effect, it would have diminished the effect of transfusion, because lower hemoglobin concentrations have been associated with higher risk of stroke. There were no strokes among children in whom the targeted decrease in hemoglobin S (to <30 percent of the total hemoglobin concentration) was occasionally not met, suggesting that brief periods of...
noncompliance with the transfusion program do not negate the benefits of prior treatment. The mechanism by which transfusion prevents stroke is not known. A reduction in hemoglobin S or an increase in total hemoglobin could have beneficial effects on cerebral vessels or interactions between erythrocytes and endothelial cells, but other factors may be involved. The rate of alloimmunization was lower in other studies in which phenotypic matching was not routine. The number of patients who discontinued receiving transfusions (10 of 63) and the frequency of missed transfusions demonstrate the difficulties with long-term transfusion therapy. The resulting rapid rise in ferritin concentrations reinforces the need to prevent iron accumulation. Che-}

It is unclear how long transfusion should be continued as a means of preventing stroke in children with sickle cell anemia. The incidence of a first stroke is highest between the ages of 2 and 5 years (1.02 per 100 patient-years), falling to 0.79 between 6 and 9 years of age, and to 0.41 between 10 and 19 years of age. The cohort study at the Medical College of Georgia showed that the risk of stroke was approximately 40 percent in the three years following abnormal results on transcranial Doppler studies, but it is unclear how long the risk remains elevated after this time without treatment. In the current trial, the risk of stroke was 10 percent per year without treatment.

The duration of the period of elevated risk is a crucial issue in deciding whether to start or continue transfusions and whether to consider bone marrow transplantation. If future studies show that transcranial Doppler ultrasonography can be used to predict the long-term risk of stroke, then the use of higher-risk therapies such as bone marrow transplantation might be reasonable. However, if treatment is needed for only a relatively short period, then the risks of bone marrow transplantation may not be justified. Alternative ways of reducing the concentrations of hemoglobin S and the use of hydroxyurea as a primary means of prevention have not been studied. Prophylactic transfusion is an important first step, but the long-term benefit of this approach may be limited by the cost and complications of transfusion.

It is likely that the risk of stroke varies among children with abnormal results on transcranial Doppler ultrasonography, but this trial was not designed to identify high-risk subgroups. Our cohort had twice as high a prevalence of MRI abnormalities as the children in the Cooperative Study of Sickle Cell Disease, who were not selected on the basis of the results of transcranial Doppler ultrasonography. The higher prevalence may indicate a causal relation or the coincidence of unrelated risk factors. Our sub-
group analysis showed that, among patients with abnormal results on Doppler studies, higher blood-flow velocities indicate a higher risk of stroke. The results of MRI did not add significantly to the predictive power of the ultrasonographic results, but this finding is not conclusive because of the small number of patients with strokes.

Some of the children with stroke had minor or transient motor findings. This is typical of children with sickle cell anemia who have a stroke, but more extensive testing often shows serious neuropsychological deficits. The patient in the transfusion group who had a stroke did not have new MRI findings. Although atypical, such findings have been reported.

Any clinical application of our findings requires an approach to transcranial Doppler screening that is similar to the one we used. Our data were obtained using similar machines and software and specially certified examiners. The risk was estimated from a single value for blood-flow velocity that represented the highest velocity in either the middle cerebral artery or the internal carotid artery. Since velocity may vary with the depth and the probe angle used, even when the sample volume is increased by increments of 2 mm, careful attention to technique is required so that the segment with the highest velocity is recorded. Examiners must be trained in this technique. We recommend evaluating all vessels in the circle of Willis to ensure anatomical orientation. A confirmatory transcranial Doppler study is required to verify that blood-flow velocity is persistently high.

The optimal frequency of transcranial Doppler screening remains to be established. Techniques vary, and comparative studies are needed to determine whether transcranial Doppler imaging devices that use different signal-acquisition paradigms provide velocity data comparable to those obtained in our study. Other tests, including MRI and magnetic resonance angiography, cannot be substituted for transcranial Doppler ultrasonography because there are currently insufficient data on the long-term risk of stroke associated with abnormalities detected by these tests.

The decision to initiate transfusion on the basis of our results should be made only after careful consideration of the risks and benefits. Blood should be matched for ABO, C, D, E, and K antigens, and the transfusions should be handled by a facility with experience with transfusion and its complications. Problems with venous access and compliance can be expected. The complications and costs of transfusion are considerable, but they are predictable and manageable. These issues must be weighed against the risk of irreversible brain damage due to stroke, the severity of which cannot be predicted. The strategy that we tested offers a way of lessening the burden of this important complication of sickle cell anemia.
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References