Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study

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The stroke prevention study in sickle cell disease (STOP) demonstrated a 90% reduction in stroke risk with transfusion among patients with time-averaged mean cerebral blood velocity (TAMV) of 200 cm/s or more as measured by transcranial Doppler (TCD). In STOP, 232 brain magnetic resonance angiograms (MRAs) were performed on 100 patients, 47 in the transfusion arm and 53 in the standard care arm. Baseline MRA findings were interpreted as normal in 75 patients and as indicating mild stenosis in 4 patients and severe stenosis in 21 patients. Among 35 patients who underwent magnetic resonance angiography within 30 days of random assignment, the TAMV was significantly higher in 7 patients with severe stenosis compared with 28 patients with normal MRA findings or mild stenosis (276.7 ± 34 vs 215 ± 15.6 cm/s; $P < .001$). In the standard care arm, 4 of 13 patients with abnormal MRA findings had strokes compared with 5 of 40 patients with normal MRA findings ($P = .03$). In this arm, TAMV became normal (less than 170 cm/s) or conditional (170-199 cm/s) in 26 of 38 patients with normal or mildly abnormal baseline MRA but remained abnormal in 8 of 10 patients with severely abnormal baseline MRA. These results suggest that TCD often detects flow abnormalities indicative of stroke risk before MRA lesions become evident. Furthermore, patients with abnormal MRA findings and higher TCD velocities are at higher risk for stroke, and their cerebral TAMVs are unlikely to decrease without transfusion. (Blood. 2004;103:2822-2826)

Introduction

Stroke is a devastating complication of sickle cell disease (SCD). Ischemic strokes are more frequent among patients younger than 20 years of age, whereas older patients experience hemorrhagic strokes.[1-3] The incidence of ischemic strokes is highest in patients with homozygous sickle cell anemia (HbSS) between 1 and 9 years of age.[1] Patients who have ischemic strokes are at high risk for recurrence unless they are placed on a regimen of chronic transfusions aimed at maintaining the level of sickle hemoglobin below 30% or 50%.[4-6] The pathophysiology of stroke in sickle cell disease remains poorly understood. Infarctive strokes are most often the result of fibrous proliferation of the intima affecting the distal internal carotid artery (dICA), the proximal middle cerebral artery (MCA), and the proximal anterior cerebral artery (ACA).[7,8] This leads to vaso-occlusion and to the development of collaterals. Definitive study of large vessel disease has required the use of cerebral angiography. This is an invasive and risky procedure for patients with SCD. Study of blood flow using magnetic resonance angiography (MRA) is a noninvasive alternative that has recently been adapted for use in patients with SCD. Three-dimensional time-of-flight MRA has been shown to correlate well with the results of angiography.[9-11] Results with this technique have been further improved, and the number of false-positive results has been decreased by the use of echo times (TEs) shorter than 5 milliseconds (J.C., unpublished observations, October 1997).

Certain clinical and laboratory findings, such as high white blood cell counts, low hemoglobin levels, and recent episodes of acute chest syndrome, have been associated with high risk for infarctive stroke.[1,2] However, until recently there were no reliable means of prospectively identifying patients at higher risk for stroke with sufficient certainty to warrant intervention. Using transcranial Doppler ultrasound (TCD), Adams et al[12] demonstrated that patients with sickle cell disease had 40% to 50% higher time-averaged mean cerebral blood velocities (TAMVs) in the large vessels of the circle of Willis than healthy controls. They also found that children with SCD whose cerebral blood velocities were above the 95th percentile were at highest risk for strokes.[13] Cerebral blood velocities several times normal for these patients were also associated with vessel stenosis.[14] These findings served as the basis for the study of stroke prevention in sickle cell disease (STOP).[15]

In the STOP study, patients with HbSS and HbSβ^0 aged 2 to 16 years were screened with TCD. TAMV was measured in the MCA, dICA, and ACA. Velocities higher than 200 cm/s and lower than 170 cm/s were considered abnormal and normal, respectively, whereas TAMVs of 170 to 199 were termed conditional. Patients with 2 separate abnormal readings in the MCA or dICA were

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randomly assigned to observation or transfusion aimed at maintaining HbS below 30%. After 24 months of observation, 10 cerebral infarctions had occurred in the standard care arm compared with 1 in the transfusion arm. This difference was highly significant (risk for stroke was 91% lower in the transfusion group) and led to early closure of the trial.

During the screening for STOP, approximately 10% of the initial patient cohort were found to have abnormal TCD findings. In this group the stroke risk was 10% a year. Thus, a significant number of patients who would not have developed strokes, at least in the near term, had to be offered transfusions to prevent stroke in those detected at risk by TCD. If imaging studies such as MRA could improve the sensitivity of TCD in predicting stroke risk, this would be of benefit to a large number of patients.[16] MRAs were performed on a large number of patients in STOP according to a standard technique. In this report we present the MRA findings in these patients and correlate them with TCD results. Although STOP was not designed to answer the crucial question of whether MRA provides added risk prediction, the findings are of interest because MRA is widely used to evaluate children with sickle cell disease.

Patients, materials, and methods

In the STOP study, 1934 children were screened and 130 with 2 abnormal TCDs performed at least 2 weeks apart were randomly assigned. Sixty-three patients were randomly assigned to the transfusion arm and 67 to the standard care arm. For patients on the transfusion arm, transfusions were started within 3 days of randomization with the aim of decreasing hemoglobin S concentrations to less than 30% over a 21-day period and maintaining this level for the duration of the study. MRA studies were not initially included in STOP but were added after the trial began. All studies were performed after informed consent was obtained at each institution.

Transcranial Doppler

TCD studies were performed using a standardized protocol modified for children with sickle cell anemia, as previously described.[12,13] Identical equipment was used (2-MHz pulsed Doppler ultrasonography, model TME TC 2000; Nicolet, Madison, WI). Maximum TAMVs in 2-mm increments in the MCA, dICA, ACA, and the posterior cerebral and basilar arteries were recorded. Results were categorized as normal, conditional, or abnormal, as described, on the basis of the highest velocities observed. To enter the study each patient had to have abnormal results on 2 TCD studies. Findings were considered abnormal only if elevated velocity was found in either the MCA or the dICA and not solely in other arteries.

Magnetic resonance angiography performance standards

Image acquisition. MRAs were performed according to a standard protocol of image acquisition using a 3-dimensional time-of-flight technique. The most important consideration was that the TE be minimized to less than 5 milliseconds, if possible. This would reduce intravox phase dispersion and the resultant loss of flow-related signal. Loss of flow-related signal can mimic or exaggerate vascular stenoses. This is particularly problematic in patients with SCD due to increased flow rates. The smallest feasible voxel size, field of view (FOV) 15 to 20 cm, a 256 × 512 matrix, and shortest obtainable echo time were used to minimize flow-related loss of vascular signal. Although both small voxel size and short echo time are important, minimizing TE should take priority over voxel size considerations; a matrix of 256 × 256 is acceptable.

Image display. All portions were photographed in sequence and were large enough so that the vascular anatomy could be worked out when maximal intensity projections (MIPs) left questions. A 24-on-1 format was recommended as the maximum for a 14 × 17 inch sheet of film. A uniform procedure was used for MIP image generation and filming.

MRA review. Primary data collected at each review were the presence or absence of vascular lesions and their locations and severity. Segments of most interest were the MCA and internal carotid artery (ICA), which served as the qualifiable segments for randomization based on TCD velocities. Comparisons were also made with previous MRA examination results to define incident lesions. All MRAs were reviewed by a panel of experts. Each study was reviewed by 2 panel members, who had no knowledge of the patient's history or treatment. For each patient the 2 readers first read the most recent study independently and reported results on separate forms. Four arterial segments—ICA, MCA, ACA, and posterior cerebral artery (PCA)—as well as the basilar artery, were rated from normal to occluded. The same 2 readers then reviewed the previous study independently and recorded any changes. The project director or data manager from the Data Coordinating Center compared the 2 forms and directed the reviewers to review films with discrepant findings until a consensus was reached. All films underwent quality review by a member of the panel.

Arterial segments were defined by the reviewers to be normal or to be mildly (25%), moderately (50%), or severely (75%) stenosed or occluded. For the purposes of this report, moderate stenosis, severe stenosis, and occlusion were grouped under the term "severe abnormality." MRAs were defined as normal or abnormal with reference to the MCA and ICA segments only. Abnormalities of other segments are discussed separately.

Statistical analysis

The proportions of patients with severe abnormalities on MRA in the 2 treatment arms were compared with a χ^2 statistic. Two-sample rank test (Wilcoxon rank sum) was used to compare baseline TCD velocities in patients with abnormal baseline MRA and those without severe abnormalities at baseline. The incidence of stroke in patients with abnormal baseline MRA was compared with stroke incidence in those with normal MRA using proportional hazards regression. This comparison was limited to patients in the standard care arm. Throughout this article, values are presented as mean ± SD.

Results

Of the 130 randomly assigned patients, 100 underwent 232 MRA studies. Forty-seven patients were in the transfusion arm, and 53 (including 3 originally randomly assigned to transfusion but whose parents or guardians refused transfusion) were in the standard care arm. Their mean ages at the time of randomization were 8.42 ± 3.42 and 8.25 ± 3.13 years, respectively, and their mean TCD velocities at the time of randomization were 223.53 ± 24.66 and 223.64 ± 29.04 cm/s, respectively (Table 1). These 100 patients did not differ from the 30 randomly assigned STOP study patients who did not have MRA (Table 2) with respect to age, TCD velocity ($P = .78$, $P = .32$ respectively, by Wilcoxon rank sum test), or sex ($P = .37$, χ^2 test).

MRA readings

Readings of the first MRA study before stroke were interpreted as normal in 75 (75%) and as indicative of mild stenosis in 4 (4%) or severe stenosis in 21 (21%) of the 100 patients studied. Among the

Table 1. Characteristics of patients

	Transfusion n = 47	Standard care n = 53
Age at random assignment, y	8.42 ± 3.42	8.25 ± 3.13
Boys/girls	22/25	22/31
TCD velocity, mean, cm/s	223.53 ± 24.66	223.64 ± 29.04
TCD velocity, median, cm/s	216	210

Patients were those for whom MRA studies were performed and who were randomly assigned on the STOP study.

Table 2. Characteristics of randomly assigned patients in STOP who did not undergo magnetic resonance angiography

	Transfusion n = 12	Standard care n = 18
Age at randomization, y	7.94 ± 4.18	8.34 ± 3.19
Boys/girls	7/5	9/9
TCD velocity, mean, cm/s	222.08 ± 37.62	220.06 ± 23.87
TCD velocity, median, cm/s	206	216

53 patients in the standard care arm, 37 had normal findings, 3 had mild abnormalities, and 13 severe abnormalities. Among the 47 patients in the transfusion arm, 38 had normal findings, 1 had a mild abnormality, and 8 had severe abnormalities. Thus, a larger proportion of patients in the standard care arm had severe abnormalities than in the transfusion arm (25% vs 17%). However, this difference was not statistically significant ($P = .36$). It was unlikely that the difference was the result of transfusions because among patients who underwent magnetic resonance angiography within 30 days of randomization, more patients had MRA abnormalities in the standard care arm (5 of 16) than in the transfusion arm (1 of 12). The distribution of MRA and TCD abnormalities in the ICA and MCA is summarized in Table 3. Most patients (79) had normal MRA findings. There were 31, 43, and 26 patients with bilateral, left-sided, and right-sided TCD abnormalities, respectively, as opposed to 3, 14, and 3 patients with bilateral, left-sided, and right-sided MRA abnormalities, respectively. Abnormalities in other vessels were also evaluated. Among 37 patients who underwent magnetic resonance angiography within 30 days of randomization or within 90 days of randomization but had not received transfusions, none had stenosis of the posterior cerebral artery, and none had basilar artery abnormalities. Two of these patients had abnormalities of the right ACA, and 3 of 36 with assessable left ACA had abnormalities.

Correlation of MRA and TCD

In general, patients with MRA abnormalities had significantly higher cerebral blood velocities as measured by TCD. This was evident when the 35 patients who underwent magnetic resonance angiography within 30 days of random assignment were analyzed (Table 4). In this group the TAMV on which randomization was based in the 7 patients with abnormal MRA findings was 276.7 ± 34 cm/s compared with 215 ± 15.6 cm/s in the 28 patients with normal or mildly abnormal MRA findings ($P < .001$).

Events in patients who underwent magnetic resonance angiography before stroke

Among the patients in the standard care arm who underwent magnetic resonance angiography before stroke, 4 of 13 with abnormal MRA findings had strokes as opposed to 5 of 40 patients with normal MRA findings. This difference was statistically significant ($P = .03$). From this sample, however, it could not be determined whether MRA findings were an independent predictive factor for stroke because MRA abnormalities were associated with higher cerebral blood velocities. Very high cerebral blood velocities were highly predictive of stroke, thus confounding the question of the independent predictive power of the MRA.

Table 3. Distribution of MRA and TCD abnormalities in MCA and ICA

MRA	TCD Bilateral	Left	Right	Total
Bilateral abnormality	2	1	0	3
Left abnormality	5	7	2	14
Right abnormality	0	2	1	3
Normal	22	34	23	79
Inevaluable	1	0	0	1
Total	31	43	26	100

The inevaluable MRA finding with bilateral TCD abnormalities was classified as severe MRA for the study, but it could not be classified as right, left, or bilateral MRA.

Table 4. TCD velocities and MRA results in 35 patients who had MRA within 30 days of random assignment

Vessel	MRA reading	N	TAMV, cm/s
R MCA/ICA	1	31	220.4 ± 20.2
	2	1	202
	3	3	308.3 ± 18.5
L MCA/ICA	1	29	217.6 ± 20.3
	2	0	0
	3	6	275 ± 36.8

MRA scores: 1 indicates normal findings; 2, mild stenosis; 3, severe stenosis/occlusion.

Changes in MRA over time

Twenty-six of the 35 patients who underwent magnetic resonance angiography within 30 days of random assignment had repeated studies. In 11 patients, the first and second studies were compared (mean, 407.6 ± 55.8 days; median, 399 days), in 8 the first and third were compared (mean, 640.1 ± 334.5 days; median, 547 days), and in 7 the first and fourth were compared (mean, 1145.4 ± 325.5 days; median, 1204 days). Results are summarized in Table 5. Among the 10 patients who initially had normal MRA findings and were randomly assigned to the transfusion arm, no new abnormalities were observed. Of the 9 patients with initially normal MRA findings and who were in the standard care arm, one new abnormality was observed. Of the 5 patients with severe abnormalities in the standard care arm, one was found to have questionable improvement on repeat studies.

Changes in TCD over time

Patients in the standard care arm had a higher probability of having normal or conditional TCD readings on repeated studies if their baseline MRA findings were normal. In the standard care arm, TAMV measurements became normal (less than 170 cm/s) or conditional (170-199 cm/s) in 26 of 38 patients with normal or mildly abnormal MRA, but they remained abnormal in 8 of 10 patients with severe MRA abnormalities at baseline. Because patients with abnormal MRA findings had significantly higher cerebral blood velocities on TCD at baseline than did patients with normal MRA results, it can be concluded that patients with lower

Table 5. Distribution of MRA findings and change over time

Study arm	Initial MRA findings (no. patients)	Last MRA findings (no. patients)
Transfusion	Normal (10)	Normal (10)
Standard care	Normal (9)	Normal (8)
		Mild abnormality (1)
Transfusion	Mild abnormality (0)	Mild abnormality (0)
Standard care	Mild abnormality (1)	Mild abnormality (1)
Transfusion	Severe abnormality (1)	Severe abnormality (1)
Standard care	Severe abnormality (5)	Mild abnormality (1)*
		Severe abnormality (4)

*Baseline MRA values classified the left ICA as category 3 (moderate stenosis); subsequent studies classified it as category 2 (mild stenosis) or 3 (unchanged).

TCD velocities were more likely to revert to normal or conditional readings. If both variables are considered, TCD alone is sufficient to predict changes in blood velocity.

MRA in patients who experienced strokes

Thirteen of the 17 patients who experienced stroke had evaluable baseline MRA readings. Findings were normal in 3 patients but showed mild abnormalities in 3 patients, bilateral severe abnormalities in 2, and unilateral severe abnormalities in 5 that correlated with the future site of infarcts. After stroke, 1 patient with normal baseline MRA findings was found to have severe abnormalities, 2 patients with initial mild abnormalities were found to have severe abnormalities or occlusion, and 3 with severe abnormalities initially were unchanged. These changes were detected during magnetic resonance angiography performed after the clinical event but are assumed to have developed sometime between the baseline study and the clinical event.

Discussion

Transcranial Doppler ultrasonography is increasingly recognized as a screening method to identify patients with sickle cell disease who are at risk for ischemic strokes.[15] In studies correlating TCD or duplex ultrasound with angiography in patients with SCD who had strokes, most stenotic lesions were correctly identified on the basis of high flow velocity.[14,17] In this report from the STOP study, we looked at the prevalence of anatomic abnormalities in patients who had abnormal cerebral blood velocities (greater than 200 cm/s). Our findings suggest that abnormal TCD findings identified 2 groups of patients. The first group was the majority of patients, who did not have severe arterial disease at the time of the test, had normal MRA findings, and had relatively low TCD velocities. The second group consisted of patients with severe arterial disease detected on MRA and much higher TCD velocities. The difference in TAMV between the 2 groups was highly significant, raising the issue of whether magnetic resonance angiography is needed if TCD data are known. TCD is optimal as a screening test for stroke risk. At present, treatment recommendations for primary stroke prevention in SCD are based solely on TCD findings. STOP did not provide data on risk detected by MRA alone, or with abnormal MRA findings and normal or conditional TCD findings, information that would be needed to replace TCD with MRA in primary prevention.

Our study was not designed to evaluate the sensitivity and specificity of TCD to detect lesions found on MRA, and MRA data on patients with normal or conditional TCD findings were not obtained. Such data would be useful despite the low risk for stroke in these patients because the few strokes that occur may represent failures of TCD that could be compensated by MRA. Others[17,18] have reported on the correlation between TCD and MRA. In one study MRA was found to be more sensitive and specific for identifying vascular lesions in patients with sickle cell disease.[18] This study was performed on patients who had already had strokes, and the TCD techniques used were different from those used in STOP. In another study, abnormal MRA findings identified a subgroup of patients at high risk for stroke among a group of patients who had abnormal velocities in several arterial segments, determined by duplex ultrasonography.[16,17] Furthermore, it has been reported that abnormal signals in long segments on MRA correlated with subclinical infarction in asymptomatic patients.[19] Similar to what we have described for MRA, the role of magnetic resonance imaging (MRI) in the evaluation of stroke risk in conjunction with TCD is also still unclear.[20,21] STOP study data showed that MRI abnormalities are associated with very high TCD velocities, and most patients with abnormal TCD findings, as defined by the 200 cm/s STOP criterion, have normal MRI results.[21]

Although TCD is optimal as a screening test, performing a second test is often desirable to allow anatomic visualization and estimation of the severity of the lesions. It is also important to note that because a small number of children lose their ultrasound window with bone maturation, making TCD uninformative, the availability of MRA may be critical for evaluating disease in them. Another clinical situation in which MRA could be helpful is in patients with advanced arterial disease with occlusion. In these patients TCD would be uninterpretable, and MRA may be helpful in distinguishing advanced disease from the technical problems of acquiring or interpreting the TCD. A potential shortcoming of our data is that in the STOP study, patients with inadequate TCD tests or low velocities at entry were not enrolled or randomly assigned. Although these constituted a small minority (2%-5% of all TCD examinations), severe arterial disease or stenosis might have been responsible for the inadequate TCD in some of these patients. In view of our findings and of the wide availability of MRA, it is reasonable to suggest that MRA be performed in all patients in whom TCD indicates risk and in children in whom an estimate of risk by TCD cannot be obtained because of technical reasons or because of the unavailability of the test.

Further study is needed to define the role of MRA, particularly the type and severity of lesion associated with degree of risk in predicting stroke. However, TCD measurements in STOP patients were likely to remain abnormal over time, regardless of treatment in patients who had abnormal MRA findings. On the other hand TCD measurements reverted to normal in many patients with normal MRA findings, mostly with treatment but also, to some extent, in the standard care arm. This suggests, but does not prove, that children who have established MRA lesions may need long-term or indefinite treatment to prevent strokes compared with children with normal MRA findings. Our data, however, did not allow us to draw any conclusions about the effect of transfusions on MRA abnormalities. These conclusions are limited by the relatively small number of patients who underwent angiography at or close to the time of random assignment, but this information may be helpful in planning treatment and in making decisions regarding the risks and benefits of transfusions for individual patients. The current STOP II study, in which patients with normal MRA findings whose TCDs normalized on transfusion are randomly assigned to continue or discontinue transfusion after 36 months, will, it is hoped, provide clearer guidelines for some of these children.

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Appendix

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