Silent Infarcts in Children With Sickle Cell Anemia and Abnormal Cerebral Artery Velocity

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Background: A substantial minority of neurologically normal children with sickle cell disease have lesions consistent with cerebral infarction as seen on magnetic resonance imaging (MRI).

Objectives: To determine if transfusion therapy affects the rate at which silent infarcts develop and to evaluate the contribution of MRI of the brain to stroke prediction by transcranial Doppler (TCD) ultrasonography.

Study Design: Children with elevated TCD ultrasonographic velocity were randomized to receive long-term transfusion therapy or standard care. Magnetic resonance imaging of the brain was obtained at randomization, annually, and with clinical neurologic events. The risk for new silent lesions and/or stroke was compared for each treatment arm.

Results: Among the 37% of subjects with silent infarcts, those receiving standard care were significantly more likely to develop new silent lesions or stroke than were those who received transfusion therapy. For subjects receiving standard care, those with lesions at baseline were significantly more likely to develop stroke or new silent lesions than those whose MRI studies showed no abnormality.

Conclusions: Transfusion therapy lowers the risk for new silent infarct or stroke for children having both abnormal TCD ultrasonographic velocity and silent infarct. However, those with both abnormalities who are not provided transfusion therapy are at higher risk for developing a new silent infarct or stroke than are those whose initial MRI showed no abnormality. The finding of a silent infarct reinforces the need for TCD ultrasonographic screening and consideration of transfusion therapy if the abnormalities are seen. Similarly, elevated TCD ultrasonographic velocity warrants MRI of the brain because children with both abnormalities seem to be at increased risk for developing new silent infarct or stroke.

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SUBJECTS AND METHODS

SUBJECTS

The STOP Trial has been described in detail. Briefly, the highest time-averaged mean velocity in the internal carotid or middle cerebral artery measured by TCD ultrasonography, was used to classify children with HbSS or sickle-β zero thalassemia between the ages of 2 and 17 years for stroke risk. Parents were offered participation in a study comparing the rate of stroke in children who were randomized to either long-term transfusion therapy or observation.

MRI STUDIES OF THE BRAIN

Magnetic resonance imaging studies of the brain were obtained shortly after randomization, annually, and at the time of clinical events. The cranial MRI protocol included axial T1-weighted image spin echo with a repetition time between 400 and 800 milliseconds, and an echo time between 10 and 30 milliseconds. Axial proton density–T2-weighted images used either conventional spin echo or fast (turbo) spin echo images approximately 5 mm thick with a minimal slice gap. Echo time was adequate to produce 2 images, 1 with the cerebrospinal fluid dark and 1 with the cerebrospinal fluid bright with a long repetition time. A coronal proton density–T2-weighted image using the same protocol was required. Lesions were classified using definitions previously outlined. Representative images are provided in the Figure.

Only those subjects who had an MRI of the brain at the time of randomization were included in this analysis. Since the question being addressed was secondary to the study, intention-to-treat analysis was not used; treatment classification was based on actual study experience. Five subjects randomized to the transfusion therapy arm were managed with standard care. The parents of 3 children refused transfusion therapy, another child was not compliant with monthly appointments, and 1 child who developed a delayed transfusion reaction could not be provided phenotypically matched blood.

For this analysis, all 5 of these patients are considered to be in the standard care treatment arm. Studies were read by a panel of 3 neuroradiologists (F.G.M., J.B., and R.Z.) who were unaware of the subjects’ clinical status or treatment arm. Two radiologists read each study separately. When readings disagreed, the study was then read by the third radiologist. When annual studies or those obtained at the time of a clinical event were read, they were compared with previously obtained images. Since equipment or imaging programs were upgraded during the course of the study, the quality of later MRI studies was frequently better than those done earlier. As a result, some lesions seen on later studies could, in retrospect, be seen on those previously reported as showing no abnormality. In that case, the earlier result was changed to reflect the new reading.

Stroke was defined as a clinical event and did not require the demonstration of structural abnormalities on MRI studies. An independent panel of neurologists reviewed clinical data from those children who developed neurologic abnormalities consistent with stroke and determined if it supported that diagnosis.

BIOSTATISTICAL METHODS

Baseline characteristics of patients with and without silent lesions at study enrollment were compared using the Wilcoxon rank sum test. The Fisher exact test was used to determine if the proportion of patients who developed stroke or new or worse silent lesions during the study, among those with silent lesions at baseline, differed in patients who received long-term transfusion therapy when compared with those who received standard care. Some patients who initially received standard care changed to transfusion therapy while others who initially began receiving transfusion therapy subsequently quit treatment during the study. A follow-up MRI from a patient who changed treatment was included in the analysis only if at least 90% of the follow-up preceding that examination was spent in one treatment arm. Proportional hazards regression was used to determine if the risk of stroke varied with the presence or absence of silent lesions at baseline in patients who received standard care during the study. Follow-up was censored when patients started transfusion therapy or at the time of their last MRI if this occurred during the first 36 months on study and they did not start transfusion therapy or sustain a stroke. An exponential survival model was used to determine if the risk of developing new or worse silent lesions varied with the presence or absence of silent lesions at baseline in the same subset. This parametric model was selected because of the interval nature of the data. Follow-up was censored at stroke, the start of transfusion therapy, or at last MRI during the first 36 months of study if neither of these occurred.

RESULTS

BASELINE LESIONS

One hundred thirty subjects were randomized. Three were excluded from this analysis: 1 had an intracranial hemorrhage at enrollment, 1 did not have an MRI at enroll-
ment, and 1 was ineligible for the study after randomization had been accomplished. Of the 127 remaining subjects, 47 (37%) had silent infarcts. These included 18 of the 56 patients who received long-term transfusion therapy and 29 of the 71 who were managed using standard care. Their baseline characteristics are listed in Table 1. Those with silent infarcts were significantly older than those who had no abnormalities on MRIs \((P = .003)\). Analyses were unaffected when age was included as a variable.

The anatomical distribution of the lesions is given in Table 2. A total of 129 lesions were identified at the baseline evaluation of 47 patients. Eleven subjects had 1 lesion, 13 had 2, and 23 (49%) had 3 or more lesions at baseline. Lesions were most common in the deep white matter or the periventricular area in the frontal lobe but almost as frequent in similar locations in the parietal lobe. No lesions were seen in the internal capsule, brainstem, or cerebellum, but 14 occurred in the basal ganglia or thalamus. Seven lesions involved the cortex, although only 2 were exclusively cortical. Lesion size varied with 44 characterized as “small punctate” areas a few millimeters in size, 59 “medium ovoid” \((0.5–1.5 \text{ cm in largest diameter})\), and 26 “large” \((\geq1.5 \text{ cm})\).

NEW LESIONS

During the 36 months of the study, 12 patients developed new or worse silent lesions and 14 others had strokes. Among those receiving transfusion therapy, one developed a new silent lesion and another had a stroke. Among those receiving standard care, 11 developed new silent lesions and 13 others developed strokes. None of the 18 patients receiving transfusion therapy who had baseline lesions seen on MRI developed new silent lesions or suffered strokes. This contrasts with the 29 with lesions seen on MRI who were given standard care, of whom 6 developed new silent lesions and 9 suffered strokes \((P<.001)\) (Table 3).
cause long-term transfusion therapy. Be- those who show no abnormalities on MRI. In one report, among 8 subjects who had no subsequent MRI only 40 were available for analysis. Comparing those 40 to the 29 patients with silent infarcts, 4 (10%) of 40 suffered strokes compared with 9 (31%) of 29 whose initial MRIs showed abnormalities (P = .02). One patient in each group had a new or worse lesion preceding the occurrence of a stroke. Therefore, there was no significant different in the occurrence of new or worse silent lesions that were seen (24%) of the 29 who had silent infarct at enrollment and 6 (15%) of the 40 whose initial MRI studies showed no abnormalities (Table 3) (P = .24).

The relationship between silent infarct and stroke in HbSS remains unclear. Silent lesions are primarily found in the deep white matter while lesions associated with strokes involve both deep white matter and cortex. For both, the geographic distribution in the brain derives from the carotid rather than the verteobasilar circulation. Although those with silent infarcts lack neurologic symptoms commonly associated with stroke, they do have abnormalities seen on neuropsychological testing, on which their scores fall between those who have had strokes and the brief observation period. Subjects who had silent infarcts at study enrollment were significantly less likely to develop new or worse lesions if they received long-term transfusion therapy. When not trans- fused, new infarcts occurred in subjects who did not have silent infarct at study enrollment at a rate similar to the new or worse lesions that occurred in those who originally had had silent infarcts (Table 3). Although the study was not designed to address the question of whether baseline lesions on MRI make an independent contribution to risk of stroke, we found that among those patients who did not receive long-term transfusion therapy, strokes were significantly more likely to occur in subjects who had silent infarcts at baseline than in those whose initial MRI showed no abnormalities (Table 3). Finally, long-term transfusion therapy prevented the occurrence of stroke and new or worse silent lesions in both groups (Table 3).

Since our study was limited to those children with an abnormally high TCD ultrasonographic velocity, our data do not allow a determination of whether the presence of silent lesions in children with HbSS with normal TCD ultrasonographic velocity and silent infarct have an increased risk for subsequent infarction. We found that the prevalence of silent infarcts in this population was 37%, approximately twice that found in the natural history study. However, since those patients with elevated TCD ultrasonographic velocities compose 10% of all children with HbSS, our data apply to only 3.7% of children with HbSS. Thus, most children with silent infarcts must have normal or conditional cerebral artery velocities. This inference is supported by observations made on children who participated in both the Cooperative Study of Sickle Cell Disease and STOP trials in which normal flow velocities were found in 12 (71%) of the 17 children who had silent infarcts. A determination of the risk implied by the presence of silent infarct independent of TCD ul-
trasonicographic normal velocities will require outcome comparisons of children with a range of TCD ultrasonographic and MRI findings.

Our data pertain to the minority (10%) of children with HbSS who have elevated TCD ultrasonographic velocities. However, their importance is underscored by the fact that most strokes are associated with that abnormality. The adverse outcome of children in this study who had silent infarcts in addition to elevated cerebral artery velocity reinforces the need to perform TCD ultrasonography in these young children who are initially found to have silent lesions on MRI. Outcome and treatment data are needed from children with low-risk TCD ultrasonography who have an abnormality on MRI to determine if transfusion therapy prophylaxis is needed from children with low-risk TCD ultrasonography in those children who are initially found to have silent lesions on MRI. Outcome and treatment data are needed from children with low-risk TCD ultrasonography who have an abnormality on MRI to determine if such children would benefit from transfusion therapy.

CONCLUSIONS

Although transfusion therapy prevented most new silent infarcts in this study, the relationship between TCD ultrasonographic velocity and silent infarct as predictors for stroke is complex and further study is needed.

The risk for stroke in children who have both abnormalities is higher than for those with TCD ultrasonographic abnormality alone. Children with both abnormalities should be strongly considered for transfusion therapy prophylaxis.

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