Effects of Total Hemoglobin and Hemoglobin S Concentration on Cerebral Blood Flow During Transfusion Therapy to Prevent Stroke in Sickle Cell Disease

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Background The standard treatment of stroke in sickle cell disease is chronic transfusion to maintain the fraction of abnormal hemoglobin (hemoglobin S [HbS]) below 20%. Risks associated with such transfusion can be reduced by allowing higher HbS levels, but the physiological consequences of this modification are unknown. Cerebral blood flow is elevated in sickle cell disease proportionate to the degree of anemia and is reduced by transfusion. We tested the effects of various HbS levels on cerebral blood flow during the course of transfusion therapy.

Case Descriptions We monitored cerebral blood flow (by the 133Xe inhalation method) in three patients whose chronic transfusion program was changed from a traditional regimen (HbS <20%) to a moderate one, allowing HbS to rise to 45% to 50% between treatments. As expected, cerebral blood flow was higher with lower hemoglobin and higher HbS concentration. However, the HbS fraction appeared to exert a separate influence on the hyperemia, independent of total hemoglobin concentration. Furthermore, cerebral blood flow was higher during the modified regimen, despite equivalent anemia.

Conclusions These results suggest caution in adapting the modified transfusion regimen. Although HbS concentrations of 50% did not cause any frank neurological sequelae, the possible consequences of the associated hyperemia over time are unknown. We conclude that larger clinical and physiological studies of moderate transfusion regimens (allowing higher concentration of HbS) are necessary before it can become standard therapy.

Key Words • anemia, sickle cell • cerebral blood flow • stroke prevention

Stroke incidence is elevated in patients with sickle cell disease (SCD), but its recurrence is preventable by chronic transfusion.1,3 Transfusion is usually aimed at keeping hemoglobin S fraction (HbS) below 20%, and lifetime treatment might be indicated in some patients.2,4,5 Possible iatrogenic complications include blood-borne transmitted disease, alloimmunization, and iron overload. A less aggressive transfusion regimen, allowing HbS to rise to 50% between transfusions, has been proposed as equally efficacious in preventing stroke recurrence.6,7 By allowing HbS to rise to 50%, such a regimen reduces the amount of blood transfused and consequently the number of donor unit exposures as well as the iron loading. This idea, although attractive, is controversial, and its safety and efficacy are unknown.

The pathophysiology of stroke in SCD and the mechanisms of action of transfusion therapy are incompletely understood. We previously reported the occurrence of cerebral hyperemia in SCD and its strong correlation with the degree of anemia.8 However, the anemia of SCD is tightly linked to the concentration of HbS, and the two usually maintain a near-perfect correlation; their respective roles in the regulation of cerebral perfusion, as well as their possible influence as risk factors for stroke, are difficult to deconfound.

We here report the first measurements of cerebral blood flow (CBF) at different HbS levels. Three patients who were on long-term transfusion for several years after a stroke chose to terminate the treatment. In all three, the transfusion program was gradually discontinued, while the patients' clinical status and cerebral perfusion were systematically observed. This offered an opportunity to study the changes in cerebral perfusion at different concentrations of total hemoglobin (Hb) and HbS. The observations during gradual withdrawal of transfusion included a range of values typical of the less aggressive transfusion regimens, thus providing data on their physiological consequences in comparison to those of more traditional regimens. We report our observations here as preliminary tests of the separate effects of total Hb versus HbS fraction, as well as preliminary data on the ability of moderate transfusion regimens to change cerebral hemodynamics.

Case Reports

Three young women with SCD (hemoglobin SS, 4 α genes) were on long-term transfusion after a cerebrovascular event. They all were placed on deferox-
amine to control transfusional hemochromatosis but were poorly compliant. For various reasons they elected to stop the transfusion program. We gradually allowed HbS concentrations to rise with a less intense transfusion regimen, monitoring the patients continuously, before the transfusion was stopped entirely.

Case 1

This patient had rheumatic fever at age 17, with residual mitral valve insufficiency. At age 21 she developed subacute bacterial endocarditis and subarachnoid hemorrhage. A long-term transfusion program, maintaining HbS below 20%, was started. Brain magnetic resonance imaging (MRI) was normal, but she developed gastric ulcer and iron overload. Subcutaneous chelation therapy became difficult, and a central catheter was placed at age 28 for intravenous chelation. During her 29th year the transfusion was tapered, and HbS was maintained between 25% and 50%. The patient developed a superior vena cava syndrome 6 months after the current observations, and the central catheter was removed with termination of transfusion. She has since been hospitalized several times for vaso-occlusive crisis (VOC) and for pneumonia.

Case 2

This patient had been on long-term transfusion since age 18, when she developed headache with mental status change, papilledema, right lower limb weakness, and urinary incontinence during VOC. Brain computed tomogram with contrast, electroencephalogram, and angiogram were normal. Her symptoms gradually resolved after exchange transfusion. Brain MRI revealed bilateral infarcts in the posterior parietal cortex and in frontal periventricular regions. She was kept on long-term transfusion, maintaining HbS concentration below 20%, but developed multiple antibodies and became progressively iron overloaded. During her 25th year, HbS concentration was maintained between 25% and 55%. Transfusions were then stopped because of difficulty in finding compatible blood. She has since been admitted to the hospital every 3 to 6 months for acute chest syndrome and for VOC.

Case 3

This patient had been on long-term transfusion since she presented with seizures and left hemiparesis at age 8. She was splenectomized at age 15 because of increased transfusion requirements. Later she also developed hepatitis (non-A, non-B) and became progressively iron overloaded. Brain MRI revealed infarcts in the high right parietal regions and the left cerebellum. During her 24th year her HbS was maintained between 25% and 50%. The transfusions were terminated at the patient's request, and her care was transferred to another hospital. She had only three episodes of mild VOC during the following year. At age 25, however, during a mild VOC, she became progressively weak and died shortly after being admitted unconscious to the nearest emergency department. Total Hb was 3 g/dL at the time of death. No autopsy was performed.

Transfusion Regimens

Transfusions were performed on an outpatient basis. Packed red blood cells with a hematocrit of 80% were transfused, with a maximum of 15 mL/kg given over 4 to 6 hours.

The three patients were on long-term transfusion for 8, 7, and 15 years, respectively, using the usual low HbS (LS) regimen, which maintained HbS below 20%. In January 1989 we introduced a high HbS (HS) transfusion regimen that allowed the HbS to rise to 50% to 55% between transfusions. At first the time between transfusion was increased to allow total Hb to fall and HbS to rise between transfusions. When HbS reached 40% we reduced the blood volume transfused to avoid the risk of hyperviscosity resulting from a combination

![Graphs showing hematologic and cerebral blood flow (CBF) changes of the three patients.](image-url)
of high HbS and high hematocrit. All three patients were maintained on this therapy for 9 to 12 months before complete discontinuation of treatment.

Brain Imaging

MRI was performed in each patient before the change of transfusion regimen. It was repeated after 6 to 8 months on the HS regimen and a year after the termination of treatment. Regional cerebral blood flow (rCBF) was quantified with the $^{133}$Xe inhalation method using a commercial system equipped with 32 detectors (Novo Diagnostic Systems, Cerebrograph 32c). The data reported here pertain to mean cortical perfusion (averaged over all regions, both hemispheres). Flow was quantified by the 6 unknown model and expressed as $fg$, the fast compartment (gray matter) flow in milliliters per 100 g per minute. This parameter is the most accurate in data of good quality and effective compartmental separation. Furthermore, this parameter is much more sensitive to the hyperemic range, as encountered here, than total flow parameters such as the initial slope index or CBF. For these reasons, our previous publications have all employed $fg$, Quality control methods were previously reported, and the blood-brain partition coefficient for xenon was adjusted for variation in Hb concentrations using the standard table.

$rCBF$ measurements were obtained in each patient five times at different phases of the transfusion history as follows: (1) midway between transfusions while on the LS regimen; (2) midway between transfusions while on the HS regimen; (3) immediately before a transfusion while on the HS regimen; (4) 24 hours after the same transfusion while on the HS regimen; and (5) untreated, off transfusion for at least 12 months.

Results

Individual data obtained for CBF, total Hb, and percent HbS are shown in Fig 1. All patients showed wide variations of cerebral perfusion over time, and the changes were systematically related to treatment. Perfusion levels were lowest during the LS regimen (89, 92, and 107 mL/100 g per minute) and were highest when untreated patients are considered, and possibly even then secondarily to the HbS fraction.

The perfusion findings were analyzed in relation to the variation of total Hb and the HbS fraction at the time of the CBF measurement. Simple regressions of CBF on both variables are shown in Fig 2. Overall, there was a significant correlation between Hb and CBF ($r = -0.68, n = 15, P = 0.06$). There was also a significant correlation between HbS and CBF ($r = 0.80, n = 15, P = 0.003$). During transfusion therapy, however, when the circulating red blood cells were a mixture of both transfused AA cells and the patients' own SS cells, the correlation between Hb and CBF was lower ($r = 0.43, n = 12, P = NS$), whereas the correlation between CBF and HbS was still significant ($r = 0.70, n = 12, P = 0.01$). When all data (15 measurements in all three patients) were included in a stepwise multiple regression (using $F = 4.00$ to enter variables and $F = 3.96$ to remove), only percent HbS was accepted ($r = 0.80$), and this was replicated when only the data obtained during transfusion therapy were considered for the analysis ($n = 12, r = 0.70$). These results suggest that total Hb is influential only when untreated patients are considered, and possibly even then secondarily to the HbS fraction.

Hematologic data averaged during the year preceding and after the change of transfusion regimen are provided in the Table. The HS regimen was successful in decreasing the volume of transfused blood by 50 mL/kg per year, representing a decrease of more than 10 donor exposures per patient. In addition, there was a substantial reduction of iron load (>2 g/y). There are clear and significant advantages. Neurological examinations, performed at each clinic visit, remained unchanged. Repeated MRI scans did not reveal any additional lesions while on the HS regimen or 1 year after total discontinuation of therapy. No complications were detected in the three patients during the study period of less than 1 year.

Discussion

We confirm that an HS transfusion regimen, allowing a higher proportion of sickle cells between transfusions...
Hemoglobin S (HbS) concentration (50% to 55%), reduces the amount of blood transfused and donor exposure. Our limited clinical follow-up also suggests no obvious adverse events in these three patients. Identical regimens have been used in larger groups for prolonged periods of time and were reported safe. However, in the series reported by Cohen et al., although no patients had cerebral infarction, two died after intracerebral hemorrhage. One of our patients died of unknown cause approximately one year after total cessation of treatment. Thus, the possible progression of cerebrovascular disease cannot yet be entirely excluded when HbS concentrations are allowed to rise, partially or completely.

We measured CBF as an index of cerebrovascular physiology during treatment and here showed significant changes, both acutely after transfusion and during the course of therapy. Generally, CBF was higher at greater disease severity, expressed as both low Hb and high HbS. Changes in CBF after transfusion have been described in other circumstances, such as hemodialysis. However, our data suggest that in SCD the changes occurring during transfusion therapy are more complex, because the presence of HbS cells in various proportions affects the cerebrovascular circulation.

It is usually difficult to isolate the separate effects of total Hb and HbS fraction on CBF because the two are tightly linked under most circumstances. In particular, untreated patients present with extreme values of severe anemia and HbS greater than 90%. In the present study we achieved some separation by changing the transfusion method because the Hb range was similar when the patients were on the LS or the HS regimen. The results suggest a stronger influence of HbS, at least at low HbS values (below approximately 40%). As HbS was allowed to rise from the very low level achieved during the LS regimen (approximately 15%) to the higher levels allowed during the HS regimen (approximately 43%), CBF rose sharply (from a mean of 96 to 125 mL/100 g per minute) despite only a small drop of total Hb (from 9.73 to 9.33 g/dL). Furthermore, the correlation with total Hb was nonsignificant when observations in untreated patients were excluded and was found redundant in multiple regression modeling. On the other hand, the acute rise of Hb observed after transfusion (from 9.1 to 10.8 g/dL) was accompanied by a decrease of perfusion (from 138 to 117 mL/100 g per minute) despite a relatively unchanged HbS (from 37% to 28%).

These observations suggest a role of HbS concentration in determining the level of hyperemia in SCD during long-term transfusion, although total hematocrit may be more critical in affecting the acute changes immediately after a transfusion and in untreated patients. We previously speculated that the hyperemia observed in SCD plays a role in the occurrence of cerebrovascular events, particularly the ischemic events occurring in watershed areas of the brain. The current data suggest that at similar Hb concentrations a high HbS fraction contributes to increase the hyperemia and possibly could increase the likelihood of cerebrovascular damage. The generalizability of this finding is limited not only by the small number of patients but also by the fact that all three already had strokes. However, all strokes occurred many years previously, so acute changes can be ruled out, and our statistical analyses rely mainly on the changes of flow across hematologic conditions, so that infarcted areas do not substantially distort CBF values. Similarly, although end-tidal PaCO₂ seems to exhibit a systematic variation during our various treatment stages, this variation was not correlated with CBF and could not have explained the observed effects.

Although other factors are likely to be involved in the pathogenesis of cerebrovascular damage in SCD, and although we did not observe any obvious clinical deterioration in our patients related to the change of transfusion, the current findings suggest caution in the adoption of less aggressive transfusion regimens. To the extent that hyperemia in SCD may be associated with neurological sequelae, higher HbS may contribute to risks, since it was here shown to elevate CBF. This study was limited in duration (approximately 1 year) and included only three patients. Further studies are necessary to evaluate the efficacy and physiological mechanisms of moderate transfusion regimens before such regimens become standard therapy.

Acknowledgment

This study was supported in part by Public Health Service grants HL-28381 and NS-27325.

References


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*Stroke*. 1994;25:1688-1692
doi: 10.1161/01.STR.25.8.1688

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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