

## A COMPARISON OF CONSERVATIVE AND AGGRESSIVE TRANSFUSION REGIMENS IN THE PERIOPERATIVE MANAGEMENT OF SICKLE CELL DISEASE

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AND THE PREOPERATIVE TRANSFUSION IN SICKLE CELL DISEASE STUDY GROUP\*

**Abstract** *Background.* Preoperative transfusions are frequently given to prevent perioperative morbidity in patients with sickle cell anemia. There is no consensus, however, on the best regimen of transfusions for this purpose.

*Methods.* We conducted a multicenter study to compare the rates of perioperative complications among patients randomly assigned to receive either an aggressive transfusion regimen designed to decrease the hemoglobin S level to less than 30 percent (group 1) or a conservative regimen designed to increase the hemoglobin level to 10 g per deciliter (group 2).

*Results.* Patients undergoing a total of 604 operations were randomly assigned to group 1 or group 2. The severity of the disease, compliance with the protocol, and the types of operations were similar in the two groups. The preoperative hemoglobin level was 11 g per deciliter in group 1 and 10.6 g per deciliter in group 2. The preoperative value for hemoglobin S was 31 percent in group

1 and 59 percent in group 2. The most frequent operations were cholecystectomies (232), head and neck surgery (156), and orthopedic surgery (72). With the exception of transfusion-related complications, which occurred in 14 percent of the operations in group 1 and in 7 percent of those in group 2, the frequency of serious complications was similar in the two groups (31 percent in group 1 and 35 percent in group 2). The acute chest syndrome developed in 10 percent of both groups and resulted in two deaths in group 1. A history of pulmonary disease and a higher risk associated with surgery were significant predictors of the acute chest syndrome.

*Conclusions.* A conservative transfusion regimen was as effective as an aggressive regimen in preventing perioperative complications in patients with sickle cell anemia, and the conservative approach resulted in only half as many transfusion-associated complications. (*N Engl J Med* 1995;333:206-13.)

PERIOPERATIVE complications in patients with sickle cell anemia are common.<sup>1-9</sup> Early reviews reported perioperative mortality rates as high as 10 percent, and the rate of postoperative complications reached 50 percent.<sup>8,10-17</sup> These problems may arise from perioperative hypoxia, hypoperfusion, and acidosis, which cause erythrocytes to sickle, thus precipitating vaso-occlusion and organ dysfunction. To prevent these complications, transfusions of red cells are given to reduce the proportion of sickle erythrocytes and correct the anemia. Various regimens, ranging from conservative (correcting the anemia) to aggressive (lowering the level of hemoglobin S to less than 30 percent), have been used.<sup>2,4,18-21</sup> However, there is no agreement on which approach — conservative or aggressive — is better suited to the surgical treatment of patients with sickle cell anemia.<sup>1,2,6,7,9-11,18,22-34</sup>

In 1988, a multicenter study group began to address the question of perioperative care for such patients. The objective was to compare prospectively the rates of perioperative complications among patients who were randomly assigned to an aggressive or a conservative

regimen of transfusions and to determine the factors that may predict complications.

### METHODS

Patients were enrolled at 36 centers. Each institution had a principal investigator, surgeon, anesthesiologist, data coordinator, and nurse assigned to the study. A protocol was followed from enrollment through the follow-up period.

### Eligibility and Randomization

Patients were eligible for enrollment in the study if they had a diagnosis of sickle cell anemia documented by the presence of hemoglobin SS on electrophoresis, were undergoing elective surgery, and had not received a transfusion within three months before the surgery. Eligible patients were randomly assigned to undergo an aggressive regimen of transfusions designed to maintain a preoperative hemoglobin level of 10 g per deciliter (range, 9 to 11) and a hemoglobin S level of 30 percent or less (group 1) or a conservative transfusion regimen designed to maintain the hemoglobin level at 10 g per deciliter (range, 9 to 11), regardless of the percentage of hemoglobin S (group 2).

### Patient Population

From 1988 through 1993, data were collected on 692 surgical procedures randomly assigned to group 1 or group 2. Eighty-eight of these procedures were subsequently excluded from the study (42 in group 1 and 46 in group 2).

The types of surgery, demographic characteristics of the patients, and reasons for elimination from the study (cancellation of the surgery, diagnostic error, or refusal of the patient to participate) were similar in the two groups. The age distribution of the patients whose procedures were excluded was representative of that of the whole sample. A total of 551 patients were randomly assigned to group 1 or group 2 and underwent a total of 604 operations. Patients who had more than one operation were randomly reassigned to a treatment group for each subsequent procedure.

### Treatment Protocol

A multidisciplinary committee developed a standardized treatment protocol. An anesthesiologist met with each patient the day before the surgery. The patients received at least eight hours of preoperative

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Supported by a grant (HL-20985) from the National Preoperative Study in Sickle Cell Disease, a program of the Sickle Cell Disease Branch of the National Heart, Lung, and Blood Institute.

\*Members of the Preoperative Transfusion in Sickle Cell Disease Study Group are listed in the Appendix.

hydration, with intraoperative monitoring of temperature, blood pressure, electrocardiographic features, and oxygenation. Postoperative care included the administration of oxygen, intravenous hydration, and monitoring with pulse oximetry.

### Transfusion Protocol

Each patient's transfusion history was recorded. The presence of alloantibodies was determined with standard screening techniques<sup>35</sup> at the time of enrollment, before and after each transfusion, and when the patient left the study. All patients received blood from donors who tested negative for hemoglobin SS. Patients with prior febrile reactions to transfusion received leukocyte-depleted red cells (washed or filtered).

### Clinical and Laboratory Data

Laboratory studies included serial measurements of hemoglobin and hemoglobin S, antiglobulin tests, liver- and renal-function studies, and measurement of oxygen saturation. Chest films were also obtained. For each patient, the risk associated with the administration of anesthesia was determined on the basis of a scoring system developed by the American Society of Anesthesiologists.<sup>36</sup> Each operation was classified as low risk (e.g., repair of inguinal hernia), intermediate risk (e.g., intraabdominal surgery), or high risk (e.g., intracranial surgery), according to an established risk classification for surgical procedures.<sup>37</sup>

All complications occurring from the time of enrollment through-out a 30-day follow-up period were monitored and classified as minor (brief temperature elevations and mild wound infections), serious (complications requiring prolonged hospitalization), or life-threatening. Most complications that developed during surgery or in the recovery room (e.g., hypotension, hypoxia, and major bleeding) were classified as serious. Complications that were specifically defined included alloimmunization, painful crisis, the acute chest syndrome, neurologic events, renal complications, and fever or infection. Detailed information about these events was collected. Alloimmunization was defined as a new, clinically important red-cell antibody. Painful crisis was defined as nonsurgical pain lasting longer than 24 hours and requiring narcotic analgesia. The acute chest syndrome was defined as the presence of a new pulmonary infiltrate involving at least one full segment. A neurologic event was defined as a change in neurologic status accompanied by neurologic findings (e.g., seizure, coma, or stroke). A renal complication was defined as renal insufficiency, hematuria, or proteinuria (3+). Fever or infection was defined as a temperature higher than 38.5°C or a documented infection lasting at least 48 hours.

### Statistical Analysis

Using standard statistical methods,<sup>38</sup> we calculated that a sample of 600 patients was required to provide a power of 0.90 to detect a 50 percent reduction in the rate of complications in group 1 (10 percent) as compared with group 2 (20 percent). Analysis of complications was carried out by comparing the number of operations with and without each type of complication in the randomized groups. Univariate logistic-regression analysis was performed for 15 possible risk factors, with the presence or absence of a complication as the primary outcome variable.<sup>39</sup> Multivariate logistic-regression models included age, group assignment, and variables with significant univariate relations ( $P \leq 0.05$ ) to the event. Since 9 percent of the patients underwent more than one procedure, we adjusted all significance levels in the logistic regressions, using the model proposed by Zeger and Liang<sup>40</sup> to account for the correlation with the outcome. Data on patients' characteristics, transfusions, perioperative management, and complications were compared between groups. A chi-square or Fisher's exact test for proportions was used, confidence intervals were two-sided, and a P value of 0.05 or less was considered to indicate statistical significance.

## RESULTS

### Patient Characteristics

A total of 551 patients (278 in group 1 and 273 in group 2) underwent 604 operations; 303 procedures were randomly assigned to group 1 (the aggressive

transfusion regimen), and 301 to group 2 (the conservative transfusion regimen). There was no significant difference in the demographic or clinical characteristics of the patients in the two groups, except for a higher incidence of central nervous system disease in group 1 (Table 1).

### Transfusions

The average hemoglobin values were similar in groups 1 and 2: 8 and 7.9 g per deciliter, respectively, at the time of enrollment and 11 and 10.6 g per deciliter, respectively, before surgery. The median preoperative value for hemoglobin S was 31 percent in group 1 and 59 percent in group 2. Seventy-seven percent of the patients in group 2 received a single transfusion before surgery. In contrast, 57 percent of the patients in group 1 underwent exchange transfusions, and 30 percent received repeated transfusions to decrease the percentage of hemoglobin S. The patients in group 1 received an average of 5.0 units; children (age, birth to 9 years)

**Table 1. Base-Line Demographic and Clinical Characteristics of Patients Randomly Assigned to an Aggressive (Group 1) or Conservative (Group 2) Transfusion Regimen.\***

CHARACTERISTIC	GROUP 1 (N = 303)	GROUP 2 (N = 301)
% of patients		
Sex		
Male	54	48
Female	46	52
Age (yr)		
0–9	40	40
10–19	35	36
≥20	25	24
Anesthetic-risk score†		
2	47	48
3	51	51
4	2	1
Findings on screening		
Oxygen saturation <90%	2	4
Abnormal chest film	14	13
Abnormal liver function (aspartate aminotransferase >60 U [1.0 μkat/liter])	8	11
Creatinine >1.5 mg/dl (132.6 μmol/liter) or protein >3+	5	4
Medical history		
Pulmonary disease	35	30
Asthma	8	8
Smoking	8	5
Cardiac disease	8	5
Renal disease	3	4
Central nervous system disease	11	7‡
No. of hospitalizations in previous year		
0	28	22
1–4	60	64
≥5	12	13
Transfusion history		
No. of transfusions		
0	23	25
1–10	53	54
>10	24	21
Alloimmunization	19	13
Reaction	7	5

\*The group numbers refer to operations. Percentages may not sum to 100 because of rounding.

†The anesthetic risk was scored according to the system established by the American Society of Anesthesiologists; 2 denotes mild-to-moderate systemic disease, 3 severe systemic disease that is not incapacitating, and 4 incapacitating illness that is a constant threat to life.<sup>36</sup>

‡P = 0.049.

received an average of 3.8 units, and adults an average of 6.1 units. The average in group 2 was 2.5 units; children received an average of 1.5 units, and adults 3.3 units. Seventy-two percent of the transfusions in group 1 and 62 percent of those in group 2 involved leukocyte-depleted red cells.

The distribution of preoperative values for hemoglobin S in the two groups overlapped. In group 1, 14 percent of the patients had preoperative hemoglobin S levels that were more than 1 SD above the mean. In about 40 percent of these patients, the percentage of hemoglobin S did not fall substantially, despite adequate exchange transfusions or repeated simple transfusions; the other 60 percent had inadequate transfusions because of calculation errors by physicians, difficulty in obtaining matched blood, or complications that precluded further transfusion. In group 2, 15 percent of the patients had preoperative hemoglobin S levels that were less than 1 SD below the mean; 42 percent of these patients required several units of packed red cells to increase their hemoglobin levels to 10 g per deciliter and therefore had significant decreases in the percentage of hemoglobin S. Most of the other patients in this group received minimal transfusion therapy. The data were analyzed according to the intention-to-treat principle, and once the random assignments had been made, the patients remained in their designated groups, regardless of their preoperative hemoglobin S values. However, the relation between hemoglobin S levels and complication rates was also analyzed.

### Perioperative Management and Surgical Risk

There were no significant differences in the perioperative care of the patients in the two groups. Eighty-two percent of the patients in group 1 and 84 percent

**Table 2. Surgical Procedures and Surgical-Risk Categories.\***

VARIABLE	GROUP 1 (N = 303)	GROUP 2 (N = 301)
	% of operations	
Types of surgery		
Cholecystectomy	36	41
Ear, nose, and throat procedure	25	26
Orthopedic procedure	11	13
Splenectomy	6	4
Herniorrhaphy	5	5
Genitourinary procedure	3	2
Obstetrical or gynecologic procedure	3	2
Skin procedure	3	2
Gastrointestinal procedure	2	2
Eye procedure	<1	2
Vascular-access procedure	2	1
Soft-tissue biopsy	2	<1
Craniotomy	<1	0
Arteriography	<1	<1
Other	<1	0
Surgical-risk category†		
1	26	23
2	73	77
3	1	0

\*The group numbers refer to operations.

†Each procedure was classified, according to an established system of surgical-risk categories, as low risk (e.g., inguinal-hernia repair), intermediate risk (e.g., intraabdominal procedure), or high risk (e.g., intracranial procedure).<sup>37</sup>

**Table 3. Serious or Life-Threatening Complications.\***

COMPLICATION	GROUP 1 (N = 303)	GROUP 2 (N = 301)
	% of operations	
Before, during, or after surgery		
Miscellaneous intraoperative event	19	20
Acute chest syndrome	11	10
Fever or infection	7	7
Miscellaneous postoperative event	6	5
Painful crisis	5	7
Neurologic event	1	1
Renal complication	1	<1
Death	1	0
Any complication	31	35
After surgery		
Acute chest syndrome	10	10
Fever or infection	7	5
Miscellaneous postoperative event	6	5
Painful crisis	4	7
Neurologic event	1	<1
Renal complication	1	<1
Death	1	0
Any complication	21	22

\*Complications associated with transfusions, which are shown in Table 5, are excluded here. The group numbers refer to operations.

of those in group 2 received preoperative hydration. All the patients in both groups were monitored intraoperatively. Eighty-two percent of the patients in group 1 and 83 percent of those in group 2 received a combination of inhalation and intravenous anesthesia. The average duration of anesthesia was 2.6 hours in group 1 and 2.5 hours in group 2. Postoperative care was also similar in the groups; 93 percent of the patients in group 1 and 92 percent of those in group 2 received oxygen; intravenous hydration was administered to 97 percent of the patients in group 1 and to 96 percent of those in group 2.

There were no significant differences between group 1 and group 2 with respect to the types of surgery that were performed or the surgical-risk scores. Over three quarters of the operations were cholecystectomies; ear, nose, and throat procedures; or orthopedic procedures (Table 2). Within these surgical categories, the two groups were matched for age, risk factors, presenting symptoms, and subtypes of surgery.

### Complications

Nine percent of the procedures in group 1 and 6 percent of those in group 2 were associated with minor complications. The most common minor complication was a brief fever. Only serious or life-threatening complications were analyzed.

Table 3 shows the serious or life-threatening complications that occurred after the start of transfusion therapy. Transfusion-associated complications are reported separately. Thirty-one percent of the procedures in group 1 and 35 percent of those in group 2 were associated with at least one complication. Except for complications related to transfusion, there was no significant difference between the two groups in terms of specific complication rates or overall complication rates according to the surgical-risk category and type of surgery.

There were 74 complications in the preoperative period, after the start of the transfusion regimen. Most of

these complications (87 percent in group 1 and 57 percent in group 2) consisted of the development of new alloantibodies or reactions to transfusion. The other preoperative complications were mainly fever or painful crises.

Intraoperative complications occurred in 19 percent of the patients. Serious blood loss (more than 10 percent of the total volume of blood) accounted for over half these complications, and the frequency was similar in the two groups (12 percent in group 1 and 10 percent in group 2).

Twenty-one percent of the operations in group 1 and 22 percent of those in group 2 were associated with at least one serious or life-threatening postoperative complication (Table 3); three quarters of the complications developed within 14 days after surgery. The frequency of the acute chest syndrome, the most common serious complication, was the same (10 percent) in the two groups. It developed an average of three days after surgery and lasted for an average of eight days. Thirty-seven percent of the patients with this complication were treated with transfusions, and 11 percent required intubation. Painful crises occurred after 5 percent of the operations, and 26 percent of the painful crises were associated with the acute chest syndrome.

There were two deaths in group 1 and none in group 2. Both deaths occurred in adults with a history of pulmonary disease. The first patient who died was a 26-year-old man with a history of the acute chest syndrome and splenic sequestration. He underwent an elective splenectomy, with a preoperative hemoglobin level of 11 g per deciliter and 30 percent hemoglobin S. Respiratory distress developed on the second postoperative day and was eventually followed by multiorgan failure. The second patient who died was a 43-year-old man with a history of recurrent acute chest syndrome and chronic lung disease. He underwent an elective hip replacement preceded by transfusions that raised the preoperative hemoglobin S level to 26 percent. His intraoperative course was complicated by blood loss requiring transfusions. Respiratory failure developed on the fourth postoperative day and progressed to multiorgan failure.

#### Predictors of Complication Rates

We attempted to identify predictors of the acute chest syndrome, pain, and any other serious or life-threatening complication by selecting 15 variables from demographic data, medical histories, laboratory results, and surgical-risk categories. In a univariate analysis, a history of pulmonary disease and a higher surgical-risk category were associated with a higher incidence of the acute chest syndrome. In a multivariate logistic regression that included these two risk factors, age, and group assignment, only a higher surgical-risk category and a history of pulmonary disease remained significant independent predictors of the acute chest syndrome (Table 4). In a univariate analysis, age and indicators of clinical severity (organ dysfunction, frequent hospitalization, extensive transfusion, and alloimmunization) were significantly related to the incidence of

painful crises. In a multivariate logistic analysis, which included these variables and the group assignment, only older age and a greater number of hospitalizations in the year before the surgery remained independent significant predictors of painful crises (Table 4). In univariate logistic analyses, age, previous central nervous system disease, frequent hospitalization, extensive transfusion, alloimmunization, surgical risk, and the preoperative hemoglobin S value were significantly related to the incidence of any serious or life-threatening complication. In the multivariate model, only older age, central nervous system disease, prior alloimmunization, and a higher surgical-risk category remained significant independent predictors of a serious or life-threatening complication.

#### Transfusion-Associated Complications

Over 7 percent of all the patients had at least one new alloantibody, and 3 percent had multiple alloantibodies (Table 5). There was a significant difference between the two groups in the frequency of new alloantibodies (group 1, 10 percent; group 2, 5 percent;  $P=0.01$ ). Alloimmunization was associated with the number of units transfused (Fig. 1). The four most common alloantibodies detected at enrollment were to antigens E (in 20 percent of the patients), K (in 13 percent), C (in 10 percent), and Fya (in 5 percent). These were also the four most frequent new alloantibodies: antigens E (in 19 percent of the patients), K (in 12 percent), C (in 14 percent), and Fya (in 5 percent). Hemolytic transfusion reactions were six times more frequent in group 1 (6 percent) than in group 2 (1 percent). Autoantibodies developed in 3 percent of the patients, most of whom were alloimmunized.

The average length of hospitalization was the same in the two groups (eight days). The average duration for a patient with one serious complication was 14 days, but the duration varied according to the specific complication: acute chest syndrome (11 days), pain (12 days), infection (19 days), neurologic event (22 days), and renal complication (36 days).

#### DISCUSSION

Many patients with sickle cell anemia require surgery for complications of the disease.<sup>41-48</sup> Despite standard perioperative care, they frequently have serious complications.<sup>8,9,25,49</sup> Prophylactic transfusions, which decrease the frequency of most complications in patients with sickle cell disease,<sup>50</sup> are also frequently given as part of perioperative management. In this study we compared an aggressive preoperative regimen of transfusions with a conservative preoperative regimen. We found that the conservative approach was as effective as the aggressive approach in preventing complications and was associated with fewer short-term complications of blood transfusion.

The Cooperative Study of Sickle Cell Disease found that 7 percent of all deaths among patients with sickle cell anemia were related to surgery.<sup>49</sup> In this review of over 1000 operations the mortality rate was 1.1 percent.<sup>49,51</sup> However, the lack of randomization and the

Table 4. Risk Factors for Perioperative Complications.\*

RISK FACTOR	COMPLICATION				
	ACUTE CHEST SYNDROME (N = 63)		PAINFUL CRISIS (N = 35)		ANY 2 OR 3 COMPLICATIONS (N = 198)
	%	odds ratio (95% CI)	%	odds ratio (95% CI)	% odds ratio (95% CI)
Age (yr)					
<10	10		1	1.0	24 1.0
10–19	9		9	9.50 (2.14–42.00)	33 1.13 (0.70–1.84)
≥20	12		9	10.21 (2.05–50.88)	47 1.80 (1.04–3.11)
History of CNS disease					
No	10		5		31 1.0
Yes	11		14		50 2.76 (1.48–5.12)
History of pulmonary disease					
No	9	1.0	5		30
Yes	14	1.86 (1.07–3.23)	8		38
History of renal or cardiac disease					
No	11		5		32
Yes	9		13		37
No. of previous hospitalizations					
0	8		2	1.0	26
1–4	10		5	2.54 (0.74–8.68)	35
≥5	15		15	5.00 (1.33–18.75)	33
Anesthetic-risk score					
2	11		6		30
3 or 4	10		6		35
No. of previous transfusions					
0	8		4		22
1–10	10		5		33
>10	15		11		43
History of alloimmunization					
No	10		5		31 1.0
Yes	11		10		43 1.88 (1.15–3.08)
Surgical-risk category					
1	5	1.0	7		24 1.0
2 or 3	12	2.97 (1.30–6.81)	6		36 1.76 (1.08–2.89)
Group assignment					
1	11		5		31
2	10		7		35
Initial hemoglobin value (g/dl)					
<9	10		6		32
≥9	12		7		37
Preoperative hemoglobin value (g/dl)					
<9	16		5		36
≥9	10		6		33
Preoperative hemoglobin S value (%)					
0–30	9		3		23
31–50	7		7		36
51–70	14		5		34
71–100	9		9		32
Preoperative chest film					
Abnormal	12		5		35
Normal	11		7		36
Preoperative oxygen saturation <90%					
No	9		6		32
Yes	14		7		29

\*Odds ratios with 95 percent confidence intervals were calculated for statistically significant predictors in the multivariate logistic analyses. CI denotes confidence interval, and CNS central nervous system. The numbers and percentages refer to operations.

common practice of using an intensive transfusion regimen in patients viewed as having a high operative risk hinder objective comparison of transfusion practices. In our randomized, prospective study, 33 percent of the patients had complications, and the mortality rate was 0.3 percent.

The acute chest syndrome, the most frequent clinical complication, developed in 10 percent of the patients in our study and was the primary factor in the two deaths. In patients who do not have sickle cell anemia, the frequency of perioperative pulmonary complications ranges from 3 to 70 percent, but most of these complications are attributable to atelectasis.<sup>52–59</sup> We excluded atelectasis from our analysis of the acute chest syndrome. In multiple studies of over 100,000 operations, the risk of serious pulmonary events is less than 1 percent; thus, patients with sickle cell anemia are at higher risk for serious perioperative pulmonary complications than the general population.<sup>36,60</sup> Our finding that a higher surgical-risk category was a predictive factor for the acute chest syndrome is probably related to changes in ventilatory functions after major surgery.<sup>61</sup> A decrease in oxygenation and ventilation–perfusion mismatching may increase the risk of pulmonary infarction and infection in patients with sickle cell anemia.<sup>62</sup> A history of pulmonary disease was also a predictive factor for the acute chest syndrome in our study, which is consistent with the finding in the general population that a history of pulmonary disease or abnormal pulmonary function may be associated with a sixfold increase in the risk of postoperative pulmonary complications.<sup>63–67</sup>

Painful crises resulting in prolonged hospitalization occurred in 5 percent of our patients. Older age and a greater number of previous hospitalizations were predictors of such crises, which underlines the importance of the medical history in planning surgery.<sup>68–71</sup>

This study demonstrates that the frequency of transfusion reactions in patients with sickle cell anemia is higher than in other patients under-

Table 5. Transfusion-Related Complications.\*

COMPLICATION	GROUP 1 (N = 303)	GROUP 2 (N = 301)	ODDS RATIO (95% CI)
	<i>no. of operations (%)</i>		
New alloantibody†	31 (10)	14 (5)	2.33 (1.21–4.49)
Hemolysis			
Immediate	3 (1)	0	
Delayed	16 (5)	4 (1)	
Allergic reaction	0	3 (1)	
Anaphylactic reaction	1 (<1)	0	
Fever	4 (1)	4 (1)	
Fluid overload resulting in respiratory distress	3 (1)	0	
Other‡	3 (1)	0	
Any complication	41 (14)	22 (7)	2.15 (1.23–3.77)

\*Odds ratios are shown only for statistically significant differences. CI denotes confidence interval. The group numbers refer to operations.

†Detection of an antibody, by standard blood-banking techniques, not noted on enrollment or in previous records.<sup>35</sup>

‡Chills, vomiting, or transient unresponsiveness; hypotension or bradycardia; or a syncopal episode.

going surgery.<sup>72</sup> In a group of 530 patients who had cardiac surgery and who underwent a transfusion regimen that was similar to the regimen we used in group 1, red-cell alloantibodies developed in only 2 percent of the patients, and no hemolytic transfusion reactions were observed.<sup>72</sup> In contrast, new red-cell antibodies developed in 10 percent of our patients in group 1, and hemolytic transfusion reactions occurred in 6 percent. Among the patients in group 2, who received half as many units of blood as the patients in group 1, the alloimmunization rate was reduced to 5 percent, and the rate of hemolytic reactions to 1 percent. The alloantibodies detected in our patients were from common antigens, confirming our previous observation<sup>73</sup> that the high incidence of alloantibodies in patients with sickle cell anemia is due in part to differences in the incidence of red-cell antigens between black patients and blood donors, who are typically white. Therefore, routine use of extended, matched transfusions could be made cost effective by decreasing the susceptibility to alloimmunization.<sup>73-75</sup>

The optimal number of transfusions required to decrease sickling in patients undergoing surgery is unknown. A growing body of evidence suggests that limited dilution of sickle cells is beneficial.<sup>51,76-80</sup> A hemoglobin S level of 30 percent has been recommended, but levels as high as 50 to 60 percent could be equally effective. Early studies of transfusion therapy demonstrated a reversal of organ dysfunction despite relatively high hemoglobin S levels.<sup>80,81</sup> In vitro studies have shown that blood flow and viscosity depend on the level of hemoglobin and the percentage of hemoglobin S.<sup>78,82-84</sup> A fixed hematocrit of 30 percent minimizes the rise in viscosity associated with higher proportions of sickle cells.<sup>83</sup> Moreover, interactions between reversibly sickled cells may increase the viscosity<sup>78</sup>; the addition of normal cells reduces these interactions, which suggests that a relatively small number of units of transfused blood can decrease sickling events in vivo. In patients with sickle cell anemia and stroke, maintaining the he-

moglobin S at 50 percent has been found to be as effective in preventing recurrent stroke as maintaining it at 30 percent.<sup>77,79,85</sup>

We did not include a group of patients who received no transfusions in this study. The consensus of the investigators was that the risk associated with no transfusion, estimated on the basis of previous data, was too high. Studies of elective surgery in patients with sickle cell anemia who did not receive transfusions suffer from the same design flaws and selection bias reviewed above. In the largest series, which included children undergoing elective major surgery, 35 percent of the patients who did not receive transfusions before

surgery had pulmonary complications, whereas none of the patients who received transfusions had such complications.<sup>86</sup> Since prophylactic transfusion therapy reduces the incidence of pulmonary disease and other complications of sickle cell anemia, we concluded that a pilot prospective trial of surgery without transfusion must be conducted before attempting a randomized trial.<sup>3,80,81,87-90</sup>

In summary, elective surgery in patients with sickle cell anemia is generally safe when performed by a multidisciplinary team. Despite optimal care, however, there is a substantial risk of morbidity, necessitating close cooperation among the medical, anesthesia, and surgical teams. A conservative transfusion regimen is as effective as an aggressive regimen in preventing perioperative complications, and a conservative approach reduces the risk of transfusion-associated complications by 50 percent.

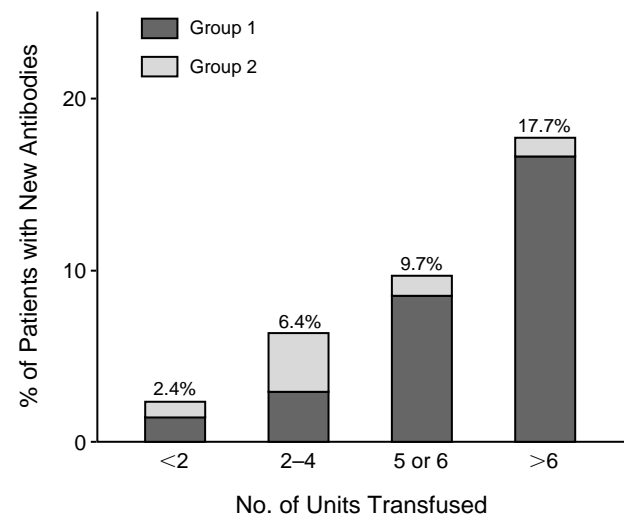


Figure 1. Percentage of Patients in Whom New Antibodies Developed, According to the Amount of Blood Transfused.

We are indebted to Shanda Robertson for data management, Bertram Lubin and Lori Styles for editorial assistance, and Jolene Edwards and Rikki Vercher-Nall for assistance in the preparation of the manuscript.

## APPENDIX

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