Obstetrical and Pediatric Anesthesia

Preoperative screening for sickle cell disease in children: clinical implications

[Dépistage préopératoire de la drépanocytose chez les enfants : implications cliniques]

Mark W. Crawford MBBS FRCPC, Seth Galton MBBS FRCA, Mohamed Abdelhaleem MD FRCPC PhD

Purpose: Preoperative screening of at-risk patients for sickle cell disease (SCD) is recommended as a method to decrease perioperative morbidity. However, the effectiveness of preoperative screening in accomplishing this goal has never been demonstrated. We undertook a retrospective study to determine the prevalence of positive test results among those screened preoperatively at our institution and to determine whether amendments to present screening guidelines can be recommended.

Methods: The hematology laboratory database of a university teaching hospital was searched to identify all patients who underwent preoperative screening for SCD from October 1999 to October 2003. The medical records of those patients testing positive were reviewed.

Results: Of 1,906 children screened preoperatively, 79 (4.1%) were diagnosed as having sickle cell trait and three (0.16%) as having some form of SCD: one had homozygous hemoglobin S and two had sickle-hemoglobin C disease. Two of the three had a family history for SCD and none had a preoperative hemoglobin concentration < 10 $g \cdot dL^{-1}$. No patient developed perioperative sickle-related complications.

Conclusion: Preoperative screening of 1,906 children identified only one asymptomatic child with undiagnosed SCD and a negative family history, suggesting that routine preoperative screening for SCD is rarely of significant clinical value in our population. Had preoperative screening not been performed, no child requiring preoperative transfusion would have been missed, representing a long-run probability of at least 99.84% that no at-risk child would require transfusion. We recommend that preoperative screening for SCD be undertaken selectively, giving consideration to the risks and benefits of screening to the individual patient.

Objectif *: Le dépistage préopératoire des patients à risque de drépanocytose est recommandé pour réduire la morbidité périopératoire. L'efficacité de ce dépistage n'a pourtant jamais été démontrée. Notre étude rétrospective voulait déterminer la prévalence de résultats positifs aux tests préopératoires à notre institution et pour déterminer si nous pouvons recommander des modifications aux présentes normes de dépistage.*

Méthode *: La base de données du laboratoire d'hématologie d'un hôpital universitaire a été revue à la recherche des patients soumis à un dépistage préopératoire de la drépanocytose entre octobre 1999 et octobre 2003. L'examen des dossiers médicaux présentant des tests positifs a été fait.*

Résultats *: Des 1 906 enfants vus en dépistage préopératoire, 79 (4,1 %) présentaient un trait drépanocytaire et 3 (0,16 %) une forme de drépanocytose : un avait une hémoglobinose S homozygote et 2 avec falciformation-hémoglobine C. Deux des trois avaient des antécédents familiaux de drépanocytose et aucun n'avait une concentration préopératoire d'hémoglobine < 10 $g \cdot dL^{-1}$. Aucune complication de falciformation ne s'est manifestée chez ces patients.*

Conclusion *: Du dépistage préopératoire de 1 906 enfants, il y avait un enfant asymptomatique atteint de drépanocytose non diagnostiquée et sans antécédents familiaux. Donc, le dépistage préopératoire de routine de la drépanocytose n'a que rarement une valeur clinique significative dans notre population. Même sans le dépistage préopératoire, aucun enfant nécessitant une transfusion préopératoire n'aurait été oublié, ce qui représente une probabilité à long terme d'au moins 99,84 % qu'aucun enfant à risque aurait eu besoin de transfusion. Le dépistage préopératoire sélectif de la drépanocytose est recommandé, tenant compte des risques et des avantages du dépistage d'un patient en particulier.*

From the Departments of Anesthesia and Pediatric Laboratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to: Dr. Mark W. Crawford, Department of Anesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Phone: 416-813-6466; Fax: 416-813-7543; E-mail: mark.crawford@sickkids.ca

Support was provided from departmental sources.

Accepted for publication March 29, 2005.

Revision accepted June 22, 2005.

SICKLE cell disease is a genetic disorder affecting diverse populations. Those at risk include African, Hispanic, Mediterranean, Middle Eastern, and Asian Indian.[1] The incidence of the heterozygous carrier state, sickle cell trait, is approximately 8%, and that of sickle cell disease approximately 0.2% in African-American newborns.[2] Sickle cell disease exhibits a wide spectrum of clinical severity resulting, in part, from various environmental factors and genetic factors that are inherited coincidentally with the β^S-globin gene.[3]

Preoperative screening to identify individuals affected with sickle cell disease is recommended as a method to decrease perioperative morbidity in populations at risk for having this hemoglobinopathy.[4–6] However, routine preoperative screening of apparently healthy patients for sickle cell disease is controversial.[7,8] The reasons are multiple, and include a lack of data demonstrating that screening has had any impact on perioperative morbidity and mortality, evidence that self-reported ethnicity is inaccurate, increasing proportions of mixed race populations, uncertainty about the reason for screening and whom to screen, and concerns that the preoperative period is an ineffective time for widespread population screening. Published guidelines on the preoperative evaluation and preparation of pediatric patients make no definite recommendations for sickle cell screening,[9] and this issue has received little attention in recent comprehensive reviews of the anesthetic management of sickle cell disease.[10,11]

The Hospital for Sick Children, Toronto, serves a population of diverse ethnicity. Preoperative screening for sickle cell disease at this hospital has traditionally been at the discretion of individual clinicians. In October 2001, the death after cholecystectomy of a 15-yr-old patient who was diagnosed in early childhood with sickle cell disease prompted the introduction of new management guidelines, mandating that all patients of African ancestry be screened before undergoing general anesthesia or sedation, regardless of their health, family history, or the planned procedure. We hypothesized that preoperative screening of all patients of African ancestry results in a low yield of positive test results in our population. Thus, we undertook the present study to determine the prevalence of positive test results among those screened preoperatively at our institution, and to determine whether amendments to present screening guidelines can be recommended.

Methods

With approval from the Research Ethics Board, the hematology laboratory database was searched to identify all surgical patients who underwent preoperative screening for sickle cell disease during the interval October 1999 to October 2003. This interval was retrospectively divided into two periods: period 1 was October 1999 until September 2001 (before the new guidelines for screening) and period 2 was October 2001 until October 2003.

The medical records of all children with positive tests on preoperative screening were reviewed. Data collected for each patient included demographics, documented family history, sickle genotype, hemoglobin concentration, type and duration of anesthesia, surgical procedure, perioperative outcome, and evidence of medical follow-up for patients diagnosed with sickle cell trait or disease. At our hospital, the laboratory uses a solubility test to screen for sickle cell disease. For confirmatory testing, abnormal samples undergo high-performance liquid chromatography (HPLC), which has quantitative capabilities and greater sensitivity and specificity than hemoglobin electrophoresis.[12–14] Infants less than six months of age are screened using HPLC only because fetal hemoglobin interferes with solubility testing. Hemoglobin analysis by HPLC is performed twice weekly in our laboratory. Data are presented as median and range, mean ± standard deviation, or percentages as appropriate.

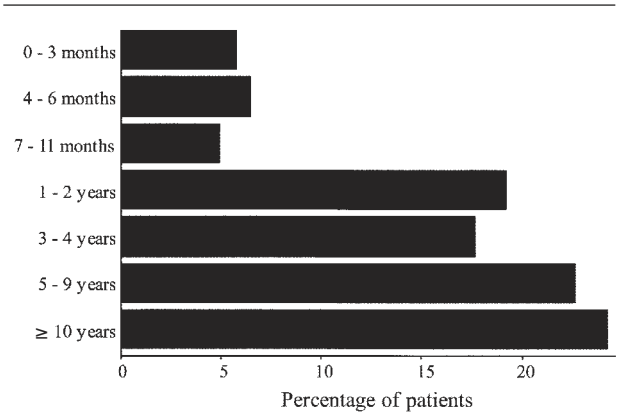

FIGURE 1 Age distribution of 1,906 pediatric patients undergoing preoperative screening for sickle cell disease during a four-year period.

Results

Overall, 1,906 children were screened for sickle cell disease before undergoing general anesthesia for any type of procedure during the four-year period. The median age of the patients was 4.5 yr (range, two days to 20 yr). The age distribution is shown in Figure 1.

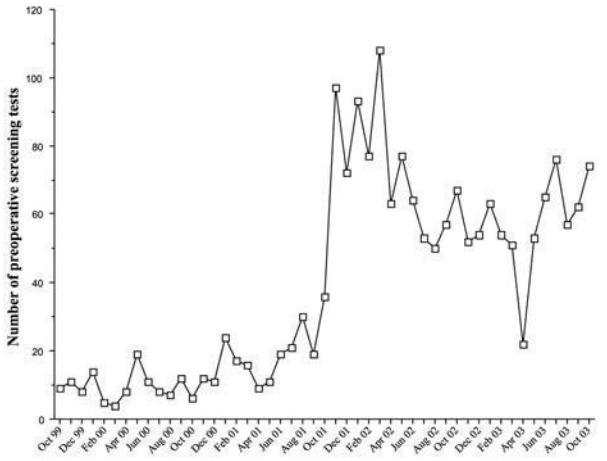

FIGURE 2 Approximate fivefold increase in the rate of preoperative screening for sickle cell disease following the introduction of mandatory screening in October 2001. The reduction in screening rate in April 2003 reflects decreased surgical caseload during the outbreak of severe acute respiratory syndrome in Toronto.

Over one-third of patients were ≤ six months or ≥ ten years of age at the time of preoperative screening.

Of the 1,906 children, 312 (16.4%) were screened in period 1 and 1,594 (83.6%) in period 2. This represents a fivefold increase in the rate of screening following the introduction of the new guidelines in October 2001 (Figure 2). Overall, 82 patients (4.3%) tested positive for the first time on preoperative screening: 14 (4.5%) of those screened in period 1 and 68 (4.3%) of those screened in period 2. Sickle cell trait was diagnosed by HPLC in 79 of the 82 patients (4.1% of all patients screened). The remaining three (0.16%), aged 2.5 to 5.9 yr, were newly diagnosed with some form of sickle cell disease: one had homozygous hemoglobin S (SS) and two had sickle-hemoglobin C (SC) disease. Case histories of these three patients are summarized in the Table. Of note, two of the three had a known family history of sickle cell disease among first- or second-degree relatives, and none had a hemoglobin concentration < 10 $g \cdot dL^{-1}$; all were scheduled to undergo minor elective surgery or diagnostic imaging. The percentage of sickle hemoglobin ranged from 44% to 70%, and that of fetal hemoglobin was 23% in the patient diagnosed with SS (Table). Patients diagnosed with sickle cell trait had a mean preoperative hemoglobin of 12 ± 1.1 $g \cdot dL^{-1}$. Fifty-two percent of children diagnosed with sickle cell trait had no documentation of relevant medical follow-up and parental genetic counseling in the medical record. There were no episodes of acute chest syndrome, vaso-occlusive crisis or other sickle-related perioperative complications.

Discussion

Preoperative screening of 1,906 patients over four years resulted in a low yield of positive test results, with only 79 patients diagnosed with sickle cell trait, one with SS disease, and two with SC disease. Of the three patients (0.16%) newly diagnosed with sickle cell disease, two had a positive family history. Thus it may be hypothesized that the incidence of sickle cell disease in our population of children with no family history is low. In addition, all three newly diagnosed patients had hemoglobin concentrations that were greater than 10 $g \cdot dL^{-1}$, and thus preoperative transfusion was not indicated for any patient according to current hospital guidelines. Had routine preoperative screening not been performed, no child needing preoperative transfusion would have been missed. This represents a long-run risk of a zero incidence for transfusion in the entire population of at least 99.84%.

Sickle cell disease is associated with significant perioperative morbidity, although reported complication rates are low for minor elective surgery and perioperative mortality is rare in patients younger than 14 yr.[15,16] Risk factors for perioperative morbidity - type of surgery, increasing age, frequency and severity of crises, pulmonary disease, and organ failure[10] - are assessable by review of the clinical history. Perioperative complication rates are similar for SS and SC disease, although the latter typically has a milder clinical phenotype.[15] Reviewing our experience over 15 years, perioperative sickle-related complications, of which the most frequent was acute chest syndrome, occurred only in patients who had a longstanding history of sickle cell disease and who were undergoing surgery for the complications of the disease, such as cholecystectomy or splenectomy.[17,18] In those retrospective studies, we encountered no sickle-related complications when the diagnosis of sickle cell disease was unknown at the time of the preoperative interview, or when it was made as a result of routine preoperative screening. These observations prompted us to question the clinical value of subjecting every child of African ancestry to preoperative venepuncture for the sole purpose of screening for sickle cell disease.

Although sickle cell disease may exist in a clinically mild form,[3] most patients with the disease are aware of the diagnosis.[4] Without newborn screening, the most common age at diagnosis is one to three years and 80 to 96% of children have been diagnosed by the age of

TABLE Case summaries of patients diagnosed with sickle cell disease as a result of preoperative screening

Patient No.	*Family history*	*Sickle genotype*	*Hb ($g \cdot dL^{-1}$)*	*Hb%*	*Co-existing diagnosis*	*Surgery*	*Perioperative outcome*
1	Positive for SS	SS	10.5	HbS% = 70	Blount's disease	Tibial osteotomy	No complications
				HbF% = 23			
				HbA2% = 7			
2	Positive for SC	SC	10.1	HbS% = 44	Trauma with orbital fracture	CT head	No complications
				HbC% = 46			
				HbF% = 6			
				HbA2% = 4			
3	None known	SC	11.2	HbS% = 47	Otitis media	Myringotomy	No complications
				HbC% = 46			
				HbF% = 5			
				HbA2% = 2			

F = female; M = male; SS = homozygous hemoglobin S; SC = sickle-hemoglobin C disease; HbS = sickle hemoglobin; HbF = fetal hemoglobin; HbA2 = hemoglobin A2; HbC = hemoglobin C; CT = computerized tomography.

ten years due to some complication.[19] The risk of a well-conducted general anesthetic in the asymptomatic child with undiagnosed sickle cell disease is unknown, but it is probably low, particularly if every patient is considered to be at risk for sickle cell disease and factors that precipitate erythrocyte sickling are avoided.[20] It is plausible that the same factors that ameliorate the clinical severity of the disease might also protect against perioperative sickle-related complications - as a consequence of differences in the degree of physiological disturbance necessary to promote sickling. For instance, a high fetal hemoglobin concentration, such as that found in the patient diagnosed with SS (23%), is associated with a protective clinical effect and low rate of acute chest syndrome.[21–23] The claim that screening all at-risk patients is justified, so that measures may be adopted to avoid factors that promote sickling should not be supported, because these factors are to be avoided for most patients and for most anesthetics.[8] Brief preoperative fasting, perioperative oxygen administration, appropriate hydration, and temperature homeostasis are essential elements of every anesthetic administered to children.

Risks associated with indiscriminate preoperative screening include unnecessary surgical cancellations, surgical delays, admissions to hospital, duplication of screening and misdiagnosis—both false-negatives and false-positives have been reported, albeit less frequently with HPLC than with hemoglobin electrophoresis.[24] Moreover, venepuncture for routine blood sampling is painful and upsetting for most children and is frequently identified as the worst part of the hospital experience.[25] The overall cost of preoperative screening including personnel, equipment, reagents and time required for screening was approximately $60 per test, although this does not include the cost of surgical delays, cancellations, or the emotional cost of a traumatic venepuncture performed under restraint.

Given that sickle cell trait typically presents no anesthetic problem, identification of this benign carrier state before anesthesia is unnecessary.[8] Our finding of an apparent lack of appropriate medical follow-up and parental counseling in over half of patients diagnosed with sickle cell trait supports the notion that the preoperative period is an ineffective time for routine screening.[26]

A retrospective study design may introduce bias, and this limitation must be considered when interpreting the results of the current study. Several factors militate against a methodologically strong study, such as a randomized controlled trial, to determine the relative safety of selective *vs* routine preopera-

tive screening for sickle cell disease in healthy at-risk children. Given that perioperative morbidity is low in this population, the sample size needed for adequate power to detect a difference in outcome is prohibitive - as large as several billion.[27] For these reasons, a randomized study of the relative merits of selective and routine screening for sickle cell disease will likely not be done, and our standards for determining the clinical value of selective screening must be less rigorous.[28] It could also be argued that the available data indicate a lack of clinical equipoise. Perhaps the strongest support for this notion is the observation that although routine screening is not performed in geographic areas where the prevalence of sickle cell disease is greatest, there are few reports of sickle-related perioperative complications among undiagnosed patients.[19,20]

In contrast, the merits of routine screening of newborns for sickle cell disease are well established, and this practice has gained widespread acceptance in parts of the United States.[14,29] Approaches to newborn screening include universal screening of all newborns regardless of race or ethnicity and targeted screening of populations at risk.[30,31] In one study, 12% of infants diagnosed with sickle cell disease as a result of universal screening were not of African ancestry and would have gone undiagnosed had targeted screening been used,[14] which is in agreement with the observation that up to 17% of infants with sickle cell disease are born to families in which neither parent is of African ancestry.[14,32] By extension, these data suggest that targeted screening of only patients of African descent in the preoperative period will be ineffective if the objective of screening is to identify every patient with sickle cell disease or trait prior to general anesthesia.

The need to screen for a disease is determined in part by the prevalence of the disease. As the prevalence of sickle cell disease varies by geographic region even within North America, it is important that care be exercised in generalizing our conclusions. Davies et al. suggested that newborn screening should be universal in areas where there are more than five cases of sickle cell disease or 150 cases of sickle cell trait per 10,000 births.[33] Pemberton et al. suggested that these guidelines could be used for preoperative screening.[5] However, our results suggest that these guidelines are inappropriate for preoperative screening. We recommend that preoperative screening for sickle cell disease be undertaken selectively, giving careful consideration to the risks and benefits of screening to the individual patient. Candidates for selective preoperative screening might include patients with a family history of sickle cell disease or those whose family history is unknown, those with known or suspected anemia, those with a history of sickle symptomatology, and at-risk patients undergoing procedures such as deliberate hypothermia with or without cardiopulmonary bypass, aortic cross-clamp, intrathoracic or upper abdominal surgery, and orthopedic procedures under tourniquet control. Routine preoperative screening for sickle cell disease is an unnecessary burden to children of African ancestry in our population.

Acknowledgement

The authors thank Mr. Paul Derksen for assistance with searching the hematology laboratory database.

References

1 *Serjeant GR, Serjeant BE.* Sickle Cell Disease, 3rd ed. Oxford: Oxford University Press; 2001: 23–8.

2 *Motulsky AG.* Frequency of sickling disorders in U.S. blacks. N Engl J Med 1973; 288: 31–3.

3 *Platt OS, Thorington BD, Brambilla DJ, et al.* Pain in sickle cell disease. Rates and risk factors. N Engl J Med 1991; 325: 11–6.

4 *Banerjee AK, Layton DM, Rennie JA, Bellingham AJ.* Safe surgery in sickle cell disease. Br J Surg 1991; 78: 516–7.

5 *Pemberton PL, Down JF, Porter JB, Bromley LM.* A retrospective observational study of pre-operative sickle cell screening. Anaesthesia 2002; 57: 334–9.

6 *Baraka A, Haddock G, Roussis X, Leventis J, Fyfe AH.* An audit of sickle cell screening in a paediatric hospital population. Scott Med J 1994; 39: 84–5.

7 *Scott-Conner CE, Brunson CD.* The pathophysiology of the sickle hemoglobinopathies and implications for perioperative management. Am J Surg 1994; 168: 268–74.

8 *Eichhorn JH.* Preoperative screening for sickle cell trait. JAMA 1988; 259: 907.

9 *Means LJ, Ferrari LR, Fisher QA, Kingston HG, Schreiner MS.* American Academy of Pediatrics, Section on Anesthesiology. Evaluation and preparation of the pediatric patients undergoing anesthesia. Pediatrics 1996; 98: 502–8.

10 *Marchant WA, Walker I.* Anesthetic management of the child with sickle cell disease. Pediatr Anaesth 2003; 13: 473–89.

11 *Firth PG, Head CA.* Sickle cell disease and anesthesia. Anesthesiology 2004; 101: 766–85.

12 *Lorey F, Cunningham G, Shafer F, Lubin B, Vichinsky E.* Universal screening for hemoglobinopathies using high-performance liquid chromatography: clinical results of 2.2 million screens. Eur J Hum Genet 1994; 2: 262–71.

13 *Sickle Cell Disease Guideline Panel.* Sickle cell disease: screening, diagnosis, management, and counseling in

newborns and infants. Clinical practice guideline number 6, Agency for Health Care Policy and Research, publication number 93-0562, Public Health Services, U.S. Department of Health and Human Services; April 1993.

14 *Shafer FE, Lorey F, Cunningham GC, Klumpp C, Vichinsky E, Lubin B.* Newborn screening for sickle cell disease: 4 years of experience from California's newborn screening program. J Pediatr Hematol Oncol 1996; 18: 36–41.

15 *Koshy M, Weiner SJ, Miller ST, et al.* Surgery and anesthesia in sickle cell disease. The Cooperative Study of Sickle Cell Disease. Blood 1995; 86: 3676–84.

16 *Delatte SJ, Hebra A, Tagge EP, Jackson S, Jacques K, Biemann Othersen H Jr.* Acute chest syndrome in the postoperative sickle cell patient. J Pediatr Surg 1999; 34: 188–92.

17 *Wales PW, Carver E, Crawford MW, Kim PC.* Acute chest syndrome after abdominal surgery in children with sickle cell disease: is a laparoscopic approach better? J Pediatr Surg 2001; 36: 718–21.

18 *Crawford MW, Speakman M, Carver ED, Kim PC.* Acute chest syndrome shows a predilection for basal lung regions on the side of upper abdominal surgery. Can J Anesth 2004; 51: 707–11.

19 *Fleming AF.* The presentation, management and prevention of crisis in sickle cell disease in Africa. Blood Reviews 1989; 3: 18–28.

20 *Oduro KA, Searle JF.* Anaesthesia in sickle-cell states: a plea for simplicity. Br Med J 1972; 4: 596–8.

21 *Platt OS, Brambilla DJ, Rosse WF, et al.* Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330: 1639–44.

22 *Castro O, Brambilla DJ, Thorington B, et al.* The acute chest syndrome in sickle cell disease. Incidence and risk factors. Blood 1994; 84: 643–9.

23 *Bunn HF.* Pathogenesis and treatment of sickle cell disease. N Eng J Med 1997; 337: 762–9.

24 *Githens JH, Lane PA, McCurdy RS, Houston ML, McKinna JD, Cole DM.* Newborn screening for hemoglobinopathies in Colorado. The first 10 years. Am J Dis Child 1990; 144: 466–70.

25 *Kolk AM, van Hoof R, Fiedeldij Dop MJ.* Preparing children for venepuncture. The effect of an integrated intervention on distress before and during venepuncture. Child Care Health Dev 2000; 26: 251–60.

26 *O'Connor ME, Drasner K.* Preoperative laboratory testing of children undergoing elective surgery. Anesth Analg 1990; 70: 176–80.

27 *Charpak Y, Blery C, Chastang C.* Designing a study for evaluating a protocol for the selective performance of preoperative tests. Stats Med 1987; 6: 813–22.

28 *Macpherson DS.* Preoperative laboratory testing: should any tests be "routine" before surgery? Med Clin North Am 1993; 77: 289–308.

29 Newborn screening for sickle cell disease and other hemoglobinopathies. Consensus conference. JAMA 1987; 258: 1205–9.

30 *Vichinsky E, Hurst D, Earles A, Earles A, Kleman K, Lubin B.* Newborn screening for sickle cell disease: effect on mortality. Pediatrics 1988; 81: 749–55.

31 *Ohene-Frempong K.* Selected testing of newborns for sickle cell disease. Pediatrics 1989; 83(5Pt2): 879–80.

32 *Mack AK.* Florida's experience with newborn screening. Pediatrics 1989; 83(5Pt2): 861–3.

33 *Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.* Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. Health Technol Assess 2000; 4: 1–99.