Elective Cholecystectomy in Children with Sickle Hemoglobinopathies

Successful Outcome Using a Preoperative Transfusion Regimen

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Twenty-seven children with major sickle hemoglobinopathies underwent elective cholecystectomy for cholelithiasis. All were managed with a preoperative transfusion regimen to achieve a hemoglobin concentration of 11–14 g/dl with greater than 65% hemoglobin A. Intraoperative cholangiography revealed common bile duct stones in five patients, although only one case was diagnosed by preoperative ultrasonographic examination. Twenty-four children underwent incidental appendectomy by total intussusception. There were no vaso-occlusive events nor any other perioperative morbidity or mortality. Four months after cholecystectomy, one boy had a small bowel obstruction requiring surgical re-exploration. No patients had transfusion-acquired infection, although one boy had erythrocyte allosensitization to Lewis A antigen. This preoperative transfusion regimen and careful perioperative management permits safe elective cholecystectomy in children with sickle cell disease.

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CHRONIC HEMOLYSIS PREDISPOSES PATIENTS with sickle cell disease to the formation of pigment (calcium bilirubinate) gallstones. Surgical management of gallstones is usually recommended even in the absence of symptoms.[1] There is, however, a reported increased risk of perioperative complications associated with general anesthesia in these patients.[2–4] Elective cholecystectomy is preferred to prevent the complications of cholelithiasis, which may necessitate an emergency cholecystectomy in an unprepared patient.[5–7] Elective surgery permits optimal perioperative support for these patients.

We report 27 children with major sickle hemoglobinopathies who completed a preoperative transfusion regimen and underwent elective cholecystectomy without mortality or morbidity. The hematologic, anesthesiologic, and surgical management of these patients is emphasized. Routine intraoperative cholangiography is recommended, as four patients had common bile duct stones not detected before surgery.

This work was supported in part by a grant from the Sickle Cell Disease Branch of the Heart, Lung, and Blood Institute, National Institutes of Health (P60-HL-28391).

Russell Ware is the recipient of Physician Scientist Award K11-HL02015.

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Materials and Methods

Patient Population

The records of all children with sickle hemoglobinopathies who underwent cholecystectomy from 1977 to 1986 were reviewed. Data were abstracted pertaining to the following: preoperative symptomatology, diagnosis, and management; perioperative surgical and anesthesia management; intraoperative findings; and postoperative complications.

Laboratory

The diagnosis of a sickle hemoglobinopathy was established by hemoglobin electrophoresis (HEP) performed on cellulose acetate (pH 8.2) and citrate agar (pH 6.2) with quantitation of hemoglobins A_2 and F. All children in this series had a diagnosis of homozygous hemoglobin S (Hb SS), heterozygous hemoglobin S and C (Hb SC), or heterozygous hemoglobin S and beta-thalassemia (Hb S B-Thal).

Imaging Procedures

Ultrasonography of the gallbladder was performed using real-time scanning. Intraoperative cholangiography was carried out through a catheter placed in the cystic duct before cholecystectomy.

Transfusion Regimen

All of our patients underwent a preoperative transfusion program to increase the percentage of hemoglobin A (Hb A) to above 65% of the total hemoglobin, while maintaining the hematocrit between 35 and 45%. In preparation for elective surgery, the child with Hb SS and baseline hemoglobin concentration of 6–9 g/dl was initially transfused with 15 ml/kg of packed red cells. One week later, an additional 15 ml/kg were administered, provided that the total hemoglobin concentration was less than 11 g/dl. Within 2 weeks, an additional transfusion was subsequently administered, after which the child was usually ready for surgery.

Partial volume exchange transfusions were occasionally necessary to avoid hyperviscosity for children with Hb SC or Hb S B-Thal, who have higher baseline hemoglobin levels than children with Hb SS. For example, a patient with Hb SC and a hemoglobin concentration of 12 g/dl would require removal of 10% of the blood volume, followed by immediate replacement with 15 ml/kg of packed erythrocytes. Partial volume exchange transfusions were performed safely in an outpatient setting and given every 2–3 weeks, until the patient achieved a hemoglobin concentration between 11 and 14 g/dl with greater than 65% Hb A.

Perioperative Management

Children were admitted to the hospital 1 day before surgery. Preoperative assessment included a complete blood count to document a hemoglobin concentration greater than 11 g/dl, a hemoglobin electrophoresis to document a hemoglobin A level greater than 65%, and a sonogram of the gallbladder to evaluate the biliary system and document the persistence of stones. On the evening before surgery, each patient was hydrated with intravenous fluids (D5 1/4NS or D5 1/2NS with 20 mEq of potassium chloride per liter) at 1.5 times the maintenance rate.

After surgery, each patient received nasal oxygen in the recovery room. A nasogastric tube remained in place until the patient regained intestinal motility. Intravenous hydration was continued at 1.5 times the maintenance rate until the patient demonstrated adequate oral intake, usually by the third postoperative day.

Results

Patient Characteristics

There were 27 black children with major sickle hemoglobinopathies who underwent cholecystectomy (Table 1). There were 19 boys and eight girls for a male predominance of 2.4:1. There were 22 children with Hb SS, two with Hb SC, and three with a Hb S B-Thal phenotype. At the time of surgery, the patients ranged in age from 3.7 to 19.2 years (mean 12.6 years, median 13.0 years).

There were 24 children who underwent primary cholecystectomy. All had experienced episodes of abdominal pain, but in many instances it was not possible to relate this pain specifically to the presence of gallstones or to distinguish it from a painful sickle cell crisis. Frequently, pain was localized to the right upper quadrant, was occasionally associated with nausea or vomiting, but was described as postprandial in only one patient. Two patients presented with acute increase in scleral icterus. Two patients with Hb SS, ages 5 and 9, and one girl with Hb SC, age 7, underwent cholecystectomy at the time of splenectomy for splenic sequestration crises. Preoperative abdominal ultrasonography revealed gallstones in each of these patients, but none of them had histories suggestive of cholecystitis.

Nineteen of the 27 patients had a total bilirubin concentration measured before surgery. The bilirubin levels ranged from 0.1 to 5.1 mg/dl (mean 2.1 mg/dl, median 1.7 mg/dl). No patients had significant elevations of the serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase.

Imaging

Twenty-five of the 27 patients had ultrasonography of the abdomen, each case demonstrating stones within the gallbladder. The bile ducts were reported as normal in 24 of these 25 patients, whereas one patient had echogenic densities consistent with stones in the common bile duct (CBD). The two patients who did not have a preoperative sonogram had plain films documenting numerous gallstones in one case, and an emphysematous gallbladder in the other. Overall, plain films of the abdomen demonstrated gallstones in five out of eight instances. Only two patients had an oral cholecystogram (OCG), and in one patient the OCG was falsely negative.

The intraoperative cholangiogram revealed filling-defects consistent with CBD stones in five children, although only one of these patients was noted to have common duct stones on preoperative ultrasonographic examination. The five patients who were found to have CBD stones at surgery had slightly lower bilirubin levels than the other patients (1.6 *vs.* 2.3, respectively).

Transfusion Regimen

The mean hemoglobin concentrations in our patient population before transfusions were the following: 8.0 g/dl for Hb SS patients; 11.9 g/dl for Hb SC patients, and 9.1 g/dl for patients with Hb S B-Thal. After completing the preoperative transfusion regimen, the mean

TABLE 1. *Patient Profile for 27 Children with a Sickle Hemoglobinopathy Who Underwent Cholecystectomy*

Patient	Sex	Age at Surgery (Years)	Hb Type	Pretransfusion Hb Concentration (g/dl)	Presurgery Hb Concentration (g/dl)	Presurgery % Hb A
1	M	3.7	SS	6.7	12.9	68
2	M	5.5	SS	8.3	12.0	78
3	M	7.7	SS	7.3	14.5	68
4	F	7.8	SC	12.0	10.8	72
5	F	8.9	SS	8.6	13.4	87
6	M	9.2	SS	8.9	13.2	85
7	M	9.4	SS	6.6	14.4	91
8	M	9.7	SS	8.1	12.6	93
9	F	11.5	SS	8.1	14.4	96
10	M	11.8	S B-Thal	8.5	12.3	81
11	F	12.2	SS	7.9	13.5	84
12	M	12.3	SC	11.8	11.7	77
13	M	12.6	SS	8.5	12.6	69
14	F	13.0	SS	7.5	14.6	76
15	M	13.7	S B-Thal	8.7	13.2	71
16	F	13.8	SS	8.6	16.3	71
17	F	14.3	SS	8.8	14.5	82
18	M	14.4	SS	9.3	13.7	79
19	M	14.5	SS	7.5	12.4	76
20	M	15.1	SS	8.4	11.9	85
21	M	15.1	SS	6.7	12.9	87
22	M	15.1	SS	8.2	11.7	96
23	M	15.1	SS	8.4	13.1	84
24	M	16.1	SS	8.1	13.8	86
25	F	18.5	S B-Thal	10.1	13.0	95
26	M	19.0	SS	8.5	14.3	72
27	M	19.2	SS	7.1	12.0	89

Key: Hb = hemoglobin; SS = hemoglobin SS; SC = hemoglobin SC; S B-Thal = hemoglobin S beta-thalassemia.

hemoglobin concentrations for each of these three patient groups were 13.4 g/dl, 11.3 g/dl, and 12.8 g/dl, respectively. The mean preoperative hemoglobin A for each group was 82%, 75%, and 82%, respectively.

Complete transfusion records were available for 21 patients. Although one patient acquired an antibody to the Lewis A antigen, the other 20 children had no evidence for alloimmunization as determined by serum antibody testing performed during the preoperative transfusion period. Thirteen of these children had additional negative serum testing for red cell antibodies, performed up to 6 months after cholecystectomy. No patient experienced clinically significant hepatitis or has expressed hematologic or clinical signs of acquired immunodeficiency syndrome.

Pathology

Numerous black pigment stones were found in each gallbladder. Histologic findings consistent with acute cholecystitis were noted in two patients, while chronic cholecystitis was noted in ten patients. Histologic examination of the remaining gallbladders was unremarkable.

Aerobic and anaerobic bacterial cultures of the bile within the gallbladder, obtained at the time of surgery, were sterile in the 20 instances that cultures were obtained.

Hospital Course

Data pertaining to hospitalization are included in Table 2. All patients initially received nitrous oxide by mask, followed by general anesthesia with halothane (12 patients), enflurane (11 patients) or isoforane (4 patients). Patients were not hyperventilated at the time of induction or during the surgical procedure. The duration of general anesthesia ranged from 110 minutes to 310 minutes (mean 184 minutes, median 175 minutes). No patients experienced perioperative hypotension, hyperventilation, hypoxia, hypothermia, or required blood products during or after surgery.

Twenty-four children underwent cholecystectomy *via* a right subcostal incision. A transverse abdominal incision was used in the three patients whose primary indication for surgery was splenic sequestration crises. Intraductal stones in four children were removed by vigorous flushing of the CBD through the cystic duct catheter. One patient required an incision in the CBD to remove stones lodged at the ampulla. An incidental appendectomy by total intussusception was performed in all but three children.[8] In two instances, the appendix could not

TABLE 2. *Hospital Course for 27 Children with a Sickle Hemoglobinopathy Who Underwent Cholecystectomy*

Patient	Surgical Procedures	Duration of Anesthesia (minutes)	Intraoperative Cholangiography Findings	Pathologic Findings	Postoperative Hospitalization (Days)	Follow-up (Months)
1	CH, AP	210	Normal	GS	7	115
2	CH, AP, SP	165	CBD Stone	GS	8	59
3	CH, AP	170	Normal	GS, CC	5	89
4	CH, AP, SP	150	Normal	GS	5	10
5	CH, AP	245	Normal	GS	16	9
6	CH	195	Normal	GS, AC	4	9
7	CH, AP	150	Normal	GS	5	49
8	CH, AP, SP	155	Normal	GS	5	10
9	CH, AP	210	Normal	GS, CC	5	56
10	CH, AP	130	Normal	GS, CC	4	19
11	CH, AP	195	Normal	GS	7	73
12	CH, AP	110	Normal	GS	5	11
13	CH, AP	310	CBD Stone	GS	9	66
14	CH, AP	255	Normal	GS, CC	6	93
15	CH, AP	180	CBD Stone	GS	7	31
16	CH	205	Normal	GS	5	93
17	CH, AP	175	Normal	GS, CC	11	48
18	CH, AP	160	Normal	GS, CC	6	63
19	CH, AP	120	Normal	GS	6	7
20	CH, AP	185	CBD Stone	GS	6	20
21	CH, AP	165	Normal	GS, CC	4	49
22	CH, AP	210	Normal	GS	4	50
23	CH, AP	170	CBD Stone	GS, CC	8	20
24	CH, AP	205	Normal	GS, CC	4	70
25	CH, AP	175	Normal	GS, AC	6	53
26	CH, AP	165	Normal	GS, CC	6	21
27	CH, AP	195	Normal	GS	7	33

Key: CH = cholecystectomy; AP = appendectomy; SP = splenectomy; CBD = common bile duct; GS = gallstones; CC = chronic cholecystitis; AC = acute cholecystitis.

be identified through the right upper quadrant incision, and one patient had a previous appendectomy at another institution.

No patients experienced vaso-occlusive crises, pneumonia, or other complications in the immediate postoperative period. The total duration of hospitalization after surgery ranged from 4 to 16 days (mean 8 days, median 6 days).

The range of follow-up in this patient population is 7 to 117 months (mean 47 months, median 51 months). To date, the only surgical complication was a small bowel obstruction 4 months after surgery, which required surgical re-exploration and lysis of adhesions.

Discussion

The sickle hemoglobinopathies are inherited hematologic disorders characterized by the presence of hemoglobin S (Hb S) and *in vivo* sickling of the erythrocytes under physiologic conditions. The molecular basis for red cell sickling is a single amino acid substitution, valine for glutamic acid, in the beta chains of the hemoglobin molecule. Upon deoxygenation, molecules of Hb S within the red cell can polymerize, giving the erythrocyte its characteristic curved or sickled shape. The principal clinical manifestations of this amino acid substitution are chronic hemolytic anemia and both acute and chronic tissue damage produced by vaso-occlusion from sickled red cells. It is the chronic hemolytic anemia which predisposes individuals with sickle cell disease to cholelithiasis.

In children with sickle hemoglobinopathies, cholelithiasis may either be asymptomatic or associated with fatty food intolerance, postprandial cramping, abdominal pain, nausea, or vomiting.[9,10] Acute cholecystitis with fever, leukocytosis, and right upper quadrant tenderness can occur, as can choledocholithiasis. Distinguishing symptoms of gallbladder disease from vaso-occlusive painful crisis by history and physical examination may often be difficult.

The prevalence of cholelithiasis in asymptomatic patients with sickle hemoglobinopathies ranges from 4 to 55%.[11-15] The lower prevalence figures are obtained using routine abdominal radiography and oral cholecystography,[11] whereas the higher figures are from studies using ultrasonography for gallstone detection.[12,13] There is a reported gender difference (female:male ratio ranging from 1 to 1.8:1), and evidence that increasing age is associated with an increased prevalence of gallstones. The hemoglobin phenotype, hemoglobin concentration, reticulocyte count, and bilirubin level have not been identified as predictive factors for cholelithiasis.[15]

Our series of patients confirms the sensitivity of the sonogram to detect cholelithiasis, but also illustrates that routine sonography will not reliably detect common bile duct stones. Five of our patients (19%) had common bile duct stones demonstrated by an intraoperative cholangiogram, but in only one patient were these stones detected by a preoperative ultrasonographic examination. Failure to detect these stones could necessitate additional surgical procedures and increase morbidity. Although intraoperative cholangiography increased the duration of general anesthesia, the cholangiogram results and the minimal complication rate justify this procedure. Similarly, the additional time required for an incidental appendectomy is justified, as acute appendicitis is difficult to differentiate from painful abdominal crises of sickle cell disease.

Previous reports have described vaso-occlusive complications and death in patients with sickle hemoglobinopathies following general anesthesia.[2–4] Several factors may have contributed to these deaths, including hypoxia, dehydration, and acidosis. In 1969, Holzmann et al.[16] reported a retrospective review of 50 patients with major sickle hemoglobinopathies who underwent general or regional anesthesia for surgical or obstetric procedures. All patients received preoperative sedation, anesthetic mixtures containing approximately 50% oxygen, and postoperative nasal oxygen. All 50 patients tolerated anesthesia well, although five had postoperative complications, including pneumonia, pulmonary infarct, and sepsis. Homi et al.[17] reported on 200 patients with a major sickle hemoglobinopathy who underwent 284 episodes of general anesthesia. Although there were 55 perioperative and postoperative complications, including six deaths, the authors concluded that the risks from general anesthesia itself were minimal.

Many of the risks of surgery and anesthesia in patients with sickle hemoglobinopathies result from vascular occlusion by sickled erythrocytes. To minimize these risks, preoperative transfusions have been advocated by some to reduce the amount of Hb S. Janik et al.[18] reported 35 children with a sickle hemoglobinopathy who underwent 46 operations, including seven cholecystectomies, all of whom received a single preoperative transfusion of 15–20 ml/kg packed erythrocytes. They reported no morbidity or mortality with this transfusion regimen. Fullerton et al.[19] reported 50 children with Hb SS who underwent 67 operations requiring general anesthesia. All received a 2-week transfusion regimen designed to achieve a preoperative Hb concentration of greater than 11 g/dl and a Hb S percentage of less than 30%. Seventeen patients underwent cholecystectomy, out of a total of 51 "major" procedures. Four patients had postoperative fever, but there were no cases of vaso-occlusive crises and no deaths. Finally, Lagarde and co-workers[20] reported 68 children who underwent 115 surgical procedures, including 11 cholecystectomies. Approximately one third of the patients received blood transfusions, but no quantitation of the Hb A percentage was made. Although 64 of the 115 procedures were "minor" or "diagnostic," there was a 44% morbidity and one death. Other authors, however, report low surgical morbidity and mortality without using preoperative transfusions.[6,17]

Our series of patients illustrates that preoperative transfusions may reduce both morbidity and mortality. We utilized a transfusion regimen designed to increase the percentage of hemoglobin A to greater than 65% of the total hemoglobin mass, while maintaining the total hemoglobin concentration between 11 and 14 g/dl. We also insured adequate perioperative hydration by using intravenous fluids at a rate of 1.5 times maintenance until patients had an adequate oral intake. None of our patients experienced vaso-occlusive complications, and there were no deaths.

Transfusion therapy, however, is not without risks. The potential hazards of blood transfusions include transmission of infectious diseases and erythrocyte allosensitization. While current routine transfusion practice includes screening for hepatitis B virus and human immunodeficiency virus, a variety of known and possibly unknown infectious agents may be transfused into the recipient. The risk of alloimmunization has been measured at 20–23% for patients with a sickle hemoglobinopathy who receive long-term transfusion.[21,22] This high prevalence is partially explained by the fact that most blood donors are white, and most of the acquired antibodies are directed against antigens that are less prevalent in the black population than in the white population.

Because of the risks associated with transfusions, prospective randomized clinical trials are warranted to define the necessity, if any, of preoperative transfusions for patients with sickle cell disease. Improvements in anesthetic techniques, intraoperative monitoring, and a heightened awareness of potential complications may reduce the risks associated with general anesthesia in these patients. Our experience describes a transfusion regimen which effectively eliminated vaso-occlusive complications, and therefore can be used for comparison to other regimens employing fewer or no transfusions.

In summary, we report 27 children with major sickle hemoglobinopathies who underwent safe elective cholecystectomy. Strict adherence to a preoperative transfusion regimen, careful anesthesia and surgery by pediatric specialists, and meticulous postoperative management insures the best possible outcome. An intraoperative cholangiogram and incidental appendectomy are useful,

and the additional anesthesia time is justified. Hematologic parameters necessary for safe elective surgery are not known, but those of our patients who achieved a Hb concentration between 11 and 14 g/dl and Hb A greater than 65% had no perioperative sickling events. Further investigation by controlled clinical trials is warranted to document the validity of our approach.

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