Open Heart Surgery in Patients With Sickle Cell Hemoglobinopathy

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Background—In patients with sickle cell trait or disease, reduced life expectancy and a tendency for complications are believed to negatively affect likelihood of survival after open heart surgery. The aim of this study was to review retrospectively the perioperative results of patients undergoing cardiac surgery at our institution.

Methods and Results—Between January 1995 and December 2006, 47 patients with either sickle cell disease or sickle cell trait underwent open heart surgery at our institution. The average age of the 29 male and 18 female patients was 20 years. Patient outcomes were analyzed through the use of the institutional database. Clinical and echocardiographic follow-up was complete in all patients except 3, with a mean follow-up period of 46 months. Current status could be confirmed in 32 patients. The most common operations included the treatment of congenital and valvular heart diseases. There were no coronary artery bypass grafting procedures. Average weight of the patients was 45 kg. Exchange transfusion was performed both preoperatively and during surgery. Mean preoperative hemoglobin S concentration was 30.4 ± 3.2% and decreased to 8.1 ± 2.6% while on pump. Average on-pump hematocrit value was 25.4 ± 3.7%; in the postoperative period, it increased to 32.7 ± 4.9%. Mean cardiopulmonary bypass and cross-clamp times were 95 and 69 minutes, respectively. None of the patients had sickling crisis or acidosis. Postoperative complications included exploration for hemorrhage in 3 patients (6.4%), stroke in 2 patients (4.3%), renal failure in 2 patients (4.3%), and prolonged ventilation in 1 patient (2.1%). Average hospital stay was 8.3 days (range, 4 to 27 days). Early in-hospital death occurred in 1 patient (2.1%); currently, 31 patients (66%) remain alive and free of cardiac symptoms.

Conclusion—Heart valve surgery and surgery for congenital heart diseases can be performed safely in patients with sickle cell disease or sickle cell trait with acceptable outcome and survival rates. (Circulation. 2010;121:14-19.)

Key Words: cardiac surgical procedures ■ exchange transfusion, whole blood ■ sickle cell anemia

Hemoglobinopathies, mainly sickle cell anemia and thalassemia, are autosomal-recessive inherited disorders. Approximately 5% of the whole world population carries a potentially pathological gene. Sickle cell disease (SCD) is frequently seen among Afro-Caribbeans but is also found in India, the Middle East, and Southern Europe. Patients with SCD who require cardiac surgery are at risk of a potentially fatal sickling crisis, which may be induced by hypothermia, hypoxia, acidosis, or low-flow states. Modification of the routine perioperative management strategies with special considerations is required for a successful outcome in patients with SCD who undergo open heart surgery.

Clinical Perspective on p 19

Because it is a rare clinical entity, literature about open heart surgery in the presence of SCD is limited to either case reports or small series. With advances in diagnostic and surgical techniques and improvements in anesthetic management skills, the number of patients with SCD who require cardiac surgery is increasing considerably. Nevertheless, literature on the evaluation and specific management of these patients remains limited, and further studies are strongly recommended.

The aim of our present study was to evaluate the outcome of open heart surgery in patients with sickle cell hemoglobinopathy at our institution. Particular emphasis was placed on perioperative complications and early (within 30 days) and late deaths.

Methods

A total of 47 patients with sickle cell hemoglobinopathy who underwent open heart surgery between January 1995 and December 2006 at our institution were evaluated in a nonrandomized, retrospective manner. During this period, a total of 13,305 patients underwent open heart surgery at our center. Of these, 6,254 were adult (>18 years of age) and 7,051 were pediatric cardiac surgical cases. Overall incidence of open heart surgical operations in patients with SCD or sickle cell trait (SCT) was 0.35% (47 of 13,305). The incidence was 0.41% (26 of 6,254) in adults and 0.29% (21 of 7,051) in the pediatric patient population. The study was conducted in
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according to the ethical principles in the Declaration of Helsinki (2000), the International Conference on Harmonisation Harmonized Tripartite Good Clinical Practice Guidelines, the policies and guidelines of the institution, and the laws of the country. Data were obtained from the medical records of all adult and pediatric patients with the diagnosis of sickle cell hemoglobinopathy who underwent cardiac surgery.

The 47 cases with SCD or SCT were investigated separately as adults and pediatric patients. The pediatric age group cutoff value was accepted as <18 years. According to age adjustment, there were 21 pediatric and 26 adult patients. Patients with SCD and patients with SCT were managed the same way. Patients received exchange transfusion before surgery, during surgery, or both. During surgery, exchange transfusion was performed during cardiopulmonary bypass (CPB) to decrease hemoglobin S (HbS) concentration to <10%.

Analyzed parameters were exchange transfusion, length of surgery, CPB time, cross-clamp time, duration of intensive care unit and hospital stays, and complications. Perioperative changes in temperature, hemodynamics, and respiratory and metabolic parameters were recorded. Alterations in hemoglobin and hematocrit, blood loss, and transfusion requirement were documented. Hemoglobin studies were performed as described previously by Heiner et al.8 Standard hemoglobin electrophoresis was performed to detect the concentrations of HbS, HbC, and HbA. All patients except 3 were followed up in the postoperative period for an average of 46 months (range, 0 to 116 months) with periodic echocardiography. Current status could be confirmed for 32 patients.

Anesthetic Management

All patients received their cardiac medications until the morning of surgery. Oral intake was stopped 6 and 4 hours before surgery in the adult and pediatric patients, respectively. Pediatric patients received intravenous maintenance fluid according to their body weight, starting from the cessation of oral intake. With glucose checkups every 2 hours and subcutaneous insulin injections as needed, diabetic adult patients were administered intravenous fluids according to their body weight, starting at the initiation of preoperative fasting.

In adult patients, sublingual lorazepam (2 mg) was administered 2 hours before surgery to decrease anxiety. Anesthesia was induced with either midazolam (0.05 to 0.1 mg/kg) and fentanyl (10 to 15 μg/kg) or thiopental 1 to 2 mg/kg and propofol 0.5 to 1 mg/kg after oxygenation. Pancuronium (0.1 mg/kg) was used for muscle relaxation. After intubation, all patients were ventilated with 100% oxygen. All invasive procedures were performed while the patients were under deep anesthesia.

In the pediatric age group, before admission to the operating theater, 2 to 4 mg/kg ketamine was injected intramuscularly. Anesthesia was induced by inhalation of sevoflurane in oxygen, and after induction, fentanyl 5 μg/kg and pancuronium 0.1 mg/kg were given. Anesthesia was maintained with isoflurane 1% in oxygen and air. After tracheal intubation, again while the patients were under deep anesthesia, arterial and central venous lines were inserted. Further incremental doses of fentanyl up to 25 μg/kg were administered during the operation.

Arterial blood pressure, central venous pressure, electrocardiogram, saturation with pulse oxymetry, and rectal temperature were routinely monitored during and after surgery. Anesthesia was maintained with isoflurane inhalation, and infusion of propofol was added at the initiation of CPB until the patients were fully awake in the postoperative period. Ultra–fast-track anesthetic management was not performed in any of the patients, and all patients were transferred to the intensive care unit while still under full anesthesia. Patients were extubated when optimal cognitive, hemodynamic, and respiratory functions were achieved. For postoperative pain management, morphine, indomethacin, and paracetamol were administered. Tranexamic acid (50 mg/kg) was used routinely to prevent bleeding complications.

Cardiopulmonary Bypass

CPB was designed in a manner to perform exchange transfusion. The bypass circuit volume was arranged to be 3 times the patient’s circulating volume (85 mL/kg) and was made up of roughly 2 U packed red blood cells, Gelofusine 500 mL (B. Braun, Melsungen, Germany), Plasma-Lyte A 400 mL (Baxter Healthcare Corporation, Deerfield, Ill), 250 mL of 5% human serum albumin, and 200 mg calcium gluconate. These volumes were adjusted according to the age, weight, and body surface area of each individual patient to reach a hematocrit value of ~30% during CPB and to decrease HbS levels to <10% of circulating hemoglobin. Additional crystalloid, colloid, or red blood cells were added to the CPB circuit as needed according to the desired hematocrit levels.

The prime was oxygenated to a PaO2 >50 kPa before the initiation of CPB, and throughout the bypass, venous oxygen saturation was kept at >80%. To avoid the risk of sickling, operations were not performed when rectal temperature was <32°C. pH of the serum during CPB was maintained between 7.34 and 7.44. The flow was adjusted as body surface area times cardiac index (2.2 to 2.4 for the adult patients; 2.4 to 3.4 for the pediatric patients). The potential risk of sickling within the coronary arteries with the administration of cold cardioplegia under the cross clamp was avoided with an initial normothermic (36°C) washout crystalloid cardioplegia dose until cardiac arrest; it was followed by a full crystalloid cardioplegia dose of 20 mL/kg at 5°C. Subsequently, 10 mL/kg crystalloid cardioplegia at 5°C was administered every 20 minutes.

To decrease the HbS concentration during surgery, in all patients before the initiation of CPB, one third to one fourth of the calculated blood volume was drained in a reservoir from the venous line, and CPB was initiated with the prime as explained earlier. Cell saver was not used, and autotransfusion was not performed during or after surgery. Red blood cells were replenished with packed red blood cells from healthy individuals obtained from the hospital blood bank.

Statistical Analysis

Statistical analyses were performed with Sigma Stat software version 3.0 (SPSS Inc, Chicago, Ill). Results are expressed as mean±standard deviation. Descriptive analysis was done for exploratory purposes only. Under the assumption that the data were normally distributed, we used the paired t test to assess the significance of the difference between conditions. Values of P<0.05 were considered statistically significant.

Results

The age range for pediatric patients was 1 to 16 years (mean, 8.2±5.3 years), with a female-to-male ratio of 7:14; the adult patients ranged in age from 18 and 46 years (mean, 30±8.5 years), with a male-to-female ratio of 15:11. Demographic data on the pediatric and adult patients are summarized in Tables 1 and 2, respectively. SCT incidence was 2 of 26 in the adult group and 2 of 21 in the pediatric group. Operations were performed to treat congenital cardiac diseases or valvular pathologies. Interestingly, none of the patients underwent coronary artery bypass grafting.

Baseline hemoglobin and hematocrit values were 8.1±2.3 g/dL and 23.4±4.7%, respectively, in the adult sickle cell group; corresponding values in the pediatric group were 9.2±2.5 g/dL and 26.3±4.4%. The preoperative HbS concentration before therapeutic exchange transfusion ranged from 64% to 85% (mean, 73.6%) and 63% to 74% (mean, 72.1%) in the adult and pediatric SCT patients, respectively. HbS concentrations were measured to be 38% and 43% in the 2 adult SCT patients and 42% and 45% in the 2 pediatric SCT patients.

Exchange transfusion was performed both preoperatively and during surgery in all patients to decrease HbS concentration and to increase hematocrit. After exchange transfusion in the preoperative period, hematocrit was increased to 31.4±3.1% in adults and 34.6±2.9% in the pediatric patients.
Mean preoperative HbS concentration in all patients (adult
and pediatric) was 30.4+/−3.2%. It decreased to 8.1+/−2.6% during
CPB. There was a statistically significant difference between
patient admission HbS concentration and preoperative HbS
concentration after exchange transfusion (P = 0.024), periopera-
tive on-pump HbS levels (P < 0.001), and postoperative HbS
concentrations (P = 0.018). Average on-pump hematocrit was
25.4+/−3.7%, which increased in the postoperative period to
32.7+/−4.9%. The difference between presurgery and postsurgery
hematocrit levels and hematocrit values during CPB was statis-
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tive, 34.2+/−4.4%; postoperative, 31.5+/−5.2%; P > 0.05).

Mean CPB and cross-clamp times were 95 and 69 minutes,
respectively. All operations were performed at ≥36°C (range,
32°C to 36°C), and the patients were actively rewarmed to
≥36°C (range, 36°C to 37.5°C) before the cessation of CPB.

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None of the patients underwent active systemic cooling, and
circulatory arrest was not used during any operation. Mean
flow rates during CPB were 5.2+/−0.7 L/min in adult patients
and 0.9+/−0.4 L/min in the pediatric group. On-pump perfu-
sion pressure ranged from 65 to 90 mm Hg (mean,
77.2+/−4.3 mm Hg) in the adult patients and from 45 to
70 mm Hg (mean, 54.1+/−3.9 mm Hg) in the pediatric group.

Neither sickling crisis nor acidosis occurred in any patient.
Postoperative complications included exploration for hemor-
hage in 3 patients (6.4%), stroke in 2 patients (4.3%), renal
failure in 2 patients (4.3%), and prolonged ventilation in 1
patient (2.1%). Average hospital stay was 8.3+/−2.8 days
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free of cardiac symptoms.
Discussion
Sickle cell hemoglobinopathy is a recessively inherited genetic disorder seen worldwide. It results from the mutation of the substitution of adenine for thymidine, which further ends up matching with valine rather than glutamine at the sixth codon of chromosome 11, ie, the \( Hb \) gene.\(^2\),\(^9\),\(^10\) The condition may present as SCD, the severe form of which is the homozygous genotype \( HbSS \), in which the fractional concentration of HbS ranges between 70% and 98%, or it can be manifested as SCT, which is rather benign and more common among populations as the heterozygous genotype \( HbAS \), in which the fractional concentration of HbS is <50%.\(^9\),\(^11\)

The solubility characteristics of HbS are severely affected, and after dispersal of oxygen to tissues, the molecule adopts its characteristic sickle shape. Erythrocytes containing high amounts of HbS undergo multiple sickling and desickling.
events, deforming their conformation and eventually resulting in autolysis and anemia.9,10 Furthermore, these deformed cells have an increased tendency to adhere to the vascular endothelium, frequently leading to occlusion of small-caliber vessels and causing organ damage. Although regarded as benign, the literature contains information about an increased rate of sudden death during high-stress activities among SCT patients.9

Expected survival rates for the patients with SCD are not well established. Age plays a major role in death rates. It is likely that the projected lifespan of patients with SCD is better now than reported in the 1960s. SCD was initially described as essentially a disease of childhood.12 Sir John Dacie stated that “the mortality is high and relatively few patients reach adult life, even when the standard of medical care is high.”12 However, a study published in 1994 challenged the widely held assumption that patients with sickle cell anemia rarely survive to adulthood by reporting that the median age at death among such patients was 42 years for men and 48 years for women in the United States.

The classic precipitating factors for sickling include stress, exposure to cold, dehydration, infections, hypoxia, inflammatory cascades, and acidosis.1–16 Such conditions lead to potassium efflux, causing formation of insoluble globin polymers. These molecules increase the viscosity of blood and lead to vasoocclusive phenomena, which include cell sickling, adherence of sickle cells to the endothelium, and vasoocclusion.8–11 Although the risks accompanying sickle cell pathology before high-risk surgery, including orthopedic and cholecystectomy, have been well stated,9 the literature contains only small series or case reports on sickle cell patients having cardiac surgery.2,3,5–16

It should be noted that above-mentioned predisposing conditions are more common in patients undergoing cardiac surgery.1–20 Especially during the operation, CPB itself, as well as aortic cross-clamping, low-flow states, topical or whole-body hypothermia, cold cardioplegia, and use of vasoconstrictive agents, may predispose to the crisis state. Hence, special care should be taken in sickle cell patients who require cardiac surgery to avoid or at least to minimize those risk factors.

These maneuvers may start with decreasing the amount of HbS concentration in the blood with exchange transfusion. Exchange transfusion decreases the amount of circulating sickle cells without increasing hematocrit levels or blood viscosity.9 On the other hand, therapeutic exchange transfusion not only is advantageous for decreasing HbS but also increases the preoperative hematocrit and hence oxygen delivery to the organs, which further facilitates surgery. Exchange transfusion can be done preoperatively, perioperatively, or both. Although there is no consensus on absolute safe values of HbS in patients undergoing surgery, it is proposed that the level of HbS should be reduced to <30% for major surgical procedures9,11 or even 5% for cardiac surgery before or at the time of surgery.15

Although some authors advocate against blood transfusion for hemoglobin levels <70 g/L,10,17–19 the benefits of a reduction in HbS and an increase in HbA concentrations are obvious for preventing sickling phenomena and providing adequate delivery of oxygen to the tissues. The advantages of preoperative transfusion include increased hematocrit levels and suppressed production of HbS in this particular group of anemic patients. The literature contains reports indicating that the majority of patients with sickle cell hemoglobinopathy scheduled for cardiac surgery receive preoperative transfusion.2,3,5–16 On the other hand, CPB itself is also a system that facilitates exchange transfusion, and using blood for priming the circuits can reconcile the aim.2,6,14,15

Blood transfusion is one of the major issues during any kind of surgery. Generally, autologous transfusion is preferred, but preoperative phlebotomy or the use of cell-saver systems during surgery could reduce the need for homologous blood transfusion. Cell-saver systems are frequently applied during cardiac surgery to conserve blood. Cell-saver systems include aspiration, a filter wash, and then retransfusion of blood to the patient. However, in patients with sickle cell hemoglobinopathy, autologous blood transfusion should be avoided for obvious reasons; furthermore, it has been shown that filtered and washed blood from the cell-saver system is more prone to sickling.2,9,11

It should be kept in mind that the amount of circulating HbS is only one factor among many (eg, disorganized endothelial function, cytokine expression, increased number of inflammatory cells) for sickling and vascular occlusion complications.9 Stress is another major factor that may lead to sickling. Cardiac surgery itself constitutes a major stress for the patient, but the preparatory phase for operation, including intubation and the insertion of catheters, contributes considerably toward this stress, particularly in pediatric patients, and it is strongly recommended that patients be kept fully sedated during this phase.11,17,18

Prevention of hypothermia in the operating theater is an easy preventive measure that is very helpful in avoiding sickling phenomena. Warm-air blankets before and after surgery may be helpful to stabilize the patient’s body temperature.11 On the other hand, systemic cooling via the CPB circuit is commonly applied in cardiac operations to reduce the metabolic rate. Hypothermia carries the risk of sickling and vascular occlusion in the presence of sickle cell hemoglobinopathy. This can be avoided by applying “topical-only” cooling or achieving moderate hypothermia, but totally warm CPB is another valid option mentioned frequently in the literature.2,3,5–7,14,15 In coronary surgery, the endomyocardial capillaries are at particular risk of occlusion by the sickling phenomena when exposed to cold cardioplegia. This can be prevented with the initial institution of warm cardioplegia to wash out the existing blood in coronary arteries, followed by cold or designated cardioplegia according to the protocols of the operating team.9,14

Avoidance of hypoxia is crucial for preventing a sickling crisis; thus, oxygen delivery to the CPB circuit should be ensured at all times during surgery. In some series, the CPB pump prime was hyperoxygenated to a PaO2 >50 kPa to mediate increased oxygen levels in the patient’s own blood after mixing in CPB circuits. The patient’s venous oxygen saturation monitoring is a reliable marker for blood oxygenation. Levels >80% during the surgical procedure were advocated as safe.2,6,15
The literature lacks consistent information on patients with sickle cell hemoglobinopathies undergoing any cardiac operations requiring CPB. Although the presence of sickle cell disorders is associated with increased risk of sickling and thus vasoocclusive complications, they should not be taken as a contraindication for cardiac surgery. Nevertheless, monitoring of certain parameters such as venous and arterial oxygen content, pH, and body temperature is mandatory for a better outcome. Furthermore, preoperative or perioperative exchange transfusion has a positive influence on the outcome of surgery and on the survival of patients undergoing cardiac surgical procedures.

Our clinical experience is consistent with the acceptance of patients with sickle cell hemoglobinopathies for cardiac surgical operations requiring CPB. Avoiding intraoperative hypoxia, hypothermia, and vasoconstrictive agents; minimizing HbS levels with preoperative and/or perioperative exchange transfusion; and ensuring a stress-free environment with the judicious use of sedatives made surgery relatively safe in this population.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Sickle cell disorders are associated with increased risk of sickling, resulting in vasoocclusive complications. The information available for patients with sickle cell hemoglobinopathies undergoing any cardiac operations using cardiopulmonary bypass is sparse. In this study, a retrospective review of 47 patients with sickle cell disease or sickle cell trait undergoing open heart surgery at a single institution over an 11-year time period demonstrated that these patients should not be denied the needed cardiac surgical treatment. Intraoperative monitoring of venous and arterial oxygen content, pH, and body temperature is critical for a successful operation. These data support the view that heart valve surgery and surgery for congenital heart diseases can be performed safely and with acceptable outcomes in patients with sickle cell disease or sickle cell trait.
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