Operative Splenectomy for Treatment of Homozygous Thalassemia Major in Afghan Children at a US Military Hospital

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Afghanistan is a war-ravaged country surrounded by mountainous terrain. Due to the geography and harsh living conditions, people have intermarried among tribes for centuries. The right familial combinations can cause manifestations of genetic linked diseases.

Thalassemia major is one of these genetic diseases that are prevalent throughout southwest Asia and Africa. This condition is so severe that if left untreated, many patients die before their fifth birthday. Modern treatments in developed countries are not available in remote regions of Afghanistan. Frequent blood transfusions and surgical removal of enlarged spleens are the only options to improve life expectancy and quality of life. US military surgical hospitals and teams frequently encountered these patients and provided surgical treatment.

Overall, surgical treatment of hypersplenism due to thalassemia major in this austere environment was highly successful. This article discusses the preoperative plan, intraoperative management, and postoperative care provided to 45 infants and children who underwent open splenectomy at a US military forward operating field hospital in Afghanistan.

Keywords: Afghanistan, Cooley anemia, humanitarian assistance, splenectomy, thalassemia.

Military Certified Registered Nurse Anesthetists (CRNAs) have been deploying to Iraq and Afghanistan in support of the current conflicts as strategic members of forward surgical teams. These teams are designed to provide lifesaving surgical capability close to the front lines of battle. Positioning medical assets far forward to the battle has decreased total mortality rates to 8.8% compared with 16.5% in the Vietnam War.[1] Current issues of providing anesthesia in a combat zone are noise pollution, sleep deprivation, and the threat of attack from enemy combatants.[2] Providing trauma and humanitarian surgery to civilians in combat zones has great implications on the battlefield. Now that current conflicts are embedded in civilian communities, winning the "hearts and minds" of the populace is extremely important for a successful campaign. One unique experience of a surgical team deployed to eastern Afghanistan was providing surgical and anesthesia care to pediatric patients who presented with hypersplenism due to β-thalassemia major (TM).

Thalassemia major is an inherited autosomal recessive disorder in the α-globin gene, located on chromosome 11.[3] Named from the Greek word for sea, it has origins near and around the Mediterranean Sea. One theory suggests that this genetic blood disorder may have some protective advantages against malaria, which is endemic to these regions of the world.[4,5] The prevalence of the β abnormality is more concentrated in people of Greek, Italian, Arab, and Jewish ethnic backgrounds. The severity is determined by homozygous (major) and heterozygous (minor) expression as well as how many genes controlling globin synthesis are defective. The manifestations of the disease are not apparent until the human physiology switches from fetal to adult hemoglobin synthesis at or around the sixth month of life. Pathophysiologic effects are widespread throughout the body, but the principal manifestation is microcytic-hypochromic hemolytic anemia. Faulty β-chain synthesis results in erythrocytes that are reduced in concentrations of hemoglobin, as well as a proliferation of free α-globin chains. These unbound α-chains precipitate in the cell and trigger phagocytosis by bone marrow leukocytes, causing premature destruction of erythrocytes and intravascular hemolysis. Premature destruction of erythroid precursors results in intramedullary death and ineffective erythropoesis.[3]

Manifestations of TM are related to 2 primary causes: anemia and iron deposition. Severe anemia if untreated has major effects on the bone marrow and cardiac systems. The cortical bone of the skeleton becomes thin as intramedullary erythroid expansion attempts to compensate with the ongoing hemolysis of red cells. Patients who are transfusion dependent may have hepatosplenomegaly, thrombocytopenia, bilirubinemia, gallstones, and viral hepatitis due to the frequency of transfusions and exposures to multiple blood donors. The chronic state of anemia and iron deposition initiates high-output congestive heart failure as well as endocrine and liver dysfunction.[3] These children demonstrate failure to

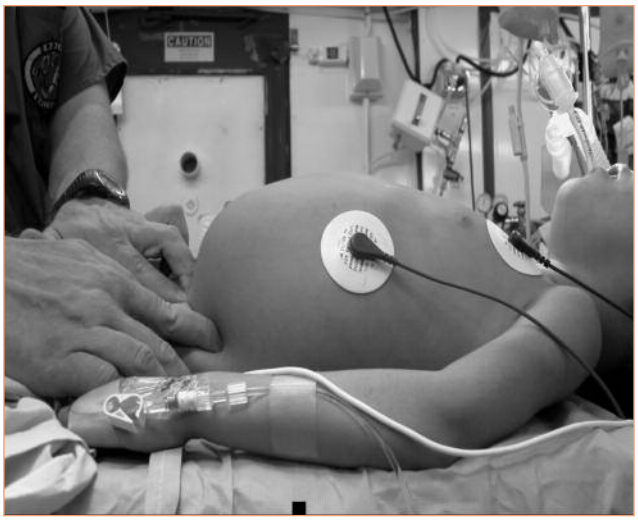

Figure 1. Six-Year-Old Afghan Boy With β-thalassemia Major Demonstrating Hypersplenism With Splenic Margins in the Extreme Left Lower Quadrant

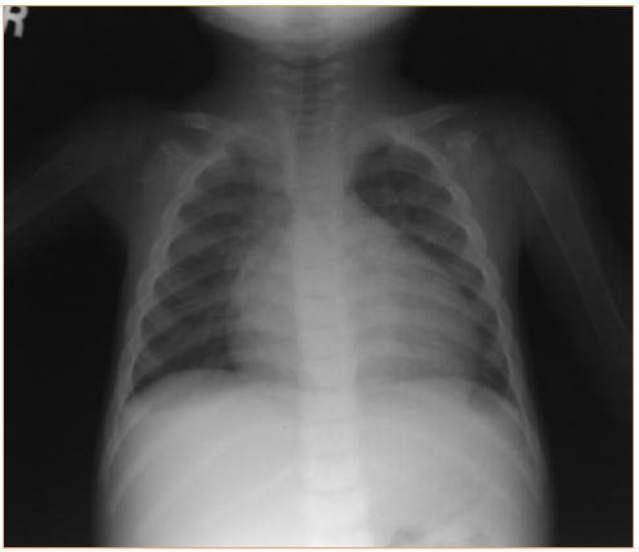

Figure 2. Preoperative Chest Radiograph of the 6-Year-Old Afghan Boy With β-thalassemia Major
Radiograph revealed cardiomegaly and elevated diaphragmatic boundaries due to hepatosplenomegaly.

thrive, bronzing of skin, and poor development compared with children without TM. If left untreated, children with TM will die before reaching the age of 5 or 6 years.

In a modern Western hospital, standard management would include blood testing in the laboratory with peripheral blood smears, as well as hemoglobin electrophoresis for α- and β-chain stability, and documentation of any history of frequent blood transfusions or iron-chelating therapies. Iron studies, bone marrow aspiration, and evaluation of fetal hemoglobin concentrations are other studies used in the differential diagnosis of TM. Imaging studies frequently show thinning of bone cortex in long bones, vertebrae, and the pelvis. One case report suggests that children with TM have difficult airway anatomy due to the cortical changes in the skull.[6] The liver and biliary tract often show evidence of hepatomegaly and gallstones. Cardiac imagery by magnetic resonance imaging (MRI) and echocardiography reveal ventricular dysfunction, fibrosis, and conduction defects due to iron overload and anemia.

Iron overload is the main cause of morbidity and mortality in patients with TM. Iron chelation is therefore essential for the optimal management of TM. Deferoxamine (Desferal) administered daily as a subcutaneous infusion has been the therapy of choice for transfusion-related iron overload and hemolysis of red blood cells.[7] Cardiac MRI and echocardiography have demonstrated an improved ventricular ejection fraction, reduction of cardiac symptoms, and decrease of 75% in liver iron concentration with continuous infusion therapies over 12 months. Achieving optimal therapeutic results depends largely on compliance, which is difficult for patients despite the severity of their disease process. Severe side effects of deferoxamine are immunosuppression, nausea, vomiting, bone pain, and cardiac changes. However, without any chelation therapy, patients will have excess iron stores and ultimately die of iron-induced cardiac disease.

Oral chelation therapies are being used in some countries, but they are reserved for patients who either have contraindications to deferoxamine or in whom deferoxamine therapy failed. Deferiprone (Ferriprox) is administered 3 times a day but has reduced iron excretion compared with deferoxamine, primarily because it has a urine-based effect and limited or no effect on iron loss from the stool. Agranulocytosis and subsequent septicemia is the major concern for patients taking this medication.[8]

Bone marrow transplant is the only definitive cure for hemoglobin diseases such as TM.[9] Stem cell transplantation has been performed in limited areas around the world. Peripheral blood stem cell transplant and bone marrow stem cell transplants have been performed in Italy and Turkey, where TM is prevalent. Before transplant, extensive hematologic evaluation was undertaken between donor and host. All patients were preconditioned with chemotherapeutic agents and methotrexate to help prevent graft-versus-host disease. Overall outcomes showed that both peripheral blood stem cell transplant and bone marrow stem cell transplant can cure some pediatric patients who have TM.[10] However, in undeveloped countries the only treatment available is a palliative surgical procedure to remove the enlarged spleen.[11]

The following information summarizes the surgical experiences in 45 infants and children with TM presenting for operative splenectomy at a US military hospital. Results are illustrated using a representative case.

Methods

• *Preoperative Evaluation and Preparation.* Taking a complete family history was the first step in the evaluation of

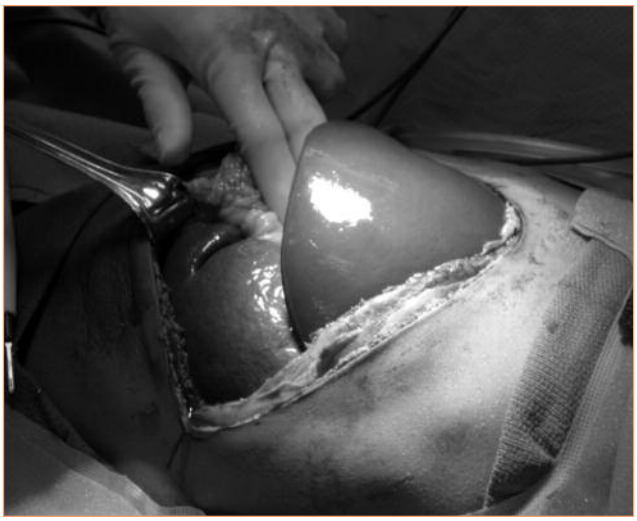

Figure 3. After a Left Upper Quadrant Subcostal Incision was Made, the Enlarged Spleen and Liver were Identified.

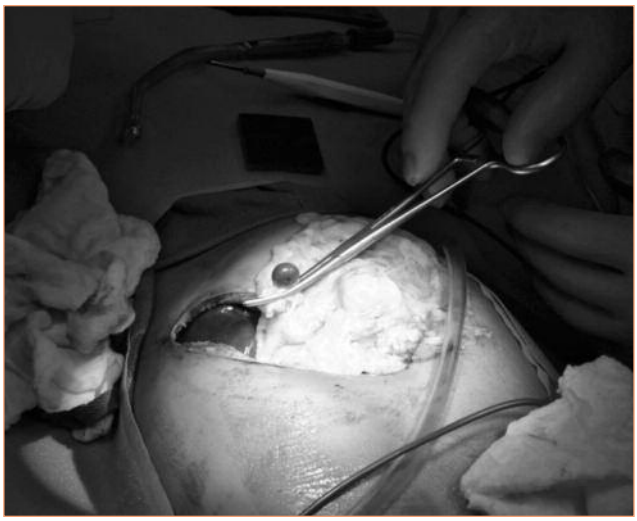

Figure 4. Exploration of Abdomen
Because accessory spleens are a common finding in patients with hypersplenism, careful exploration of the abdomen was required to prevent recurrence of hypersplenism.

the patients with TM. There were 25 boys and 20 girls who ranged in age from 13 months to 11 years (mean, 5 years). The provider could then determine the severity of the disease and formulate a preoperative plan. In Afghanistan, interpreters were used to gather information from patient's parents and family members. The most common presentation reported was the need for multiple transfusions since birth. In some cases laboratory results from Pakistan demonstrated the presence of chronic anemia. Once the examination was completed, findings would most often demonstrate spleen and liver palpitation greatly below the costal margins, indicating organomegaly (Figure 1). The children were usually fatigued, listless, and almost apathetic to needle sticks, blood draws, and testing. Electrocardiograms revealed ventricular hypertrophy, and chest radiographs showed cardiomegaly, lung congestion, and infiltrates (Figure 2).

In the field, the laboratory personnel could screen for blood type, human immunodeficiency virus (HIV), and hepatitis B and C and could obtain a baseline hemoglobin concentration, hematocrit, and platelet level. Family members were tested for compatibility if whole-blood transfusion was required since there was no access to platelets in the operating theater. Once the laboratory results were confirmed and a whole-blood donor was identified, the children were transfused 1 unit of packed red blood cells or whole blood 1 to 2 weeks before surgery to prepare them for the upcoming procedure. In addition, because of their fragile immune status and the postoperative loss of the immunoprotection of a spleen, children were vaccinated against pneumococcus, meningococcus, and *Haemophilus influenzae*.[12]

All patients were categorized as ASA physical status III or IV.

• *Intraoperative Procedure.* The day of the surgical procedure the patients presented with their parents and a whole-blood donor if needed (platelets < 100,000/mm^2).

Each child was asked through an interpreter about fluid and eating status and then placed in a gown until the surgical team was ready. The patient was taken into the operating room and placed on standard monitors.

An interpreter was present during mask induction of anesthesia with sevoflurane varying from 2% to 8% and 100% oxygen. If there was concern about aspiration, intravenous (IV) access was established, and an IV induction was performed. Once the child was anesthetized, 2 large intravenous catheters were started in the hands, feet, or saphenous veins superior to the medial malleolus. One line was dedicated for blood products, and the other for medication and fluid therapies. Most children had a 20-gauge IV line in the saphenous vein and a 22-gauge IV in the hand, but children who were small for their size required 22-gauge and 24-gauge IV catheters, respectively.

Intravenous induction was weight based and was determined by predicting postoperative pain and the duration of the procedure. Most children were given 3 to 5 µg/kg of fentanyl with a one-time dose of 1 mg/kg of rocuronium for peritoneal relaxation. Benzodiazepines preoperatively such as midazolam were not routinely given owing to the communication barrier between provider and patient. Children for the most part were stoic and apathetic to the fact that they were going to have surgery. The few patients who remained defiant and inconsolable received ketamine as an intramuscular injection and were cognitively disassociated before entering the operating room.

Intubation was performed in a standard fashion. Patients also received a small nasogastric tube to deflate the stomach away from the spleen. This was accomplished by using an adult 10F to 12F tracheal suction catheter with one end taped. An esophageal stethoscope for evaluation of heart tones and airway as well as temperature

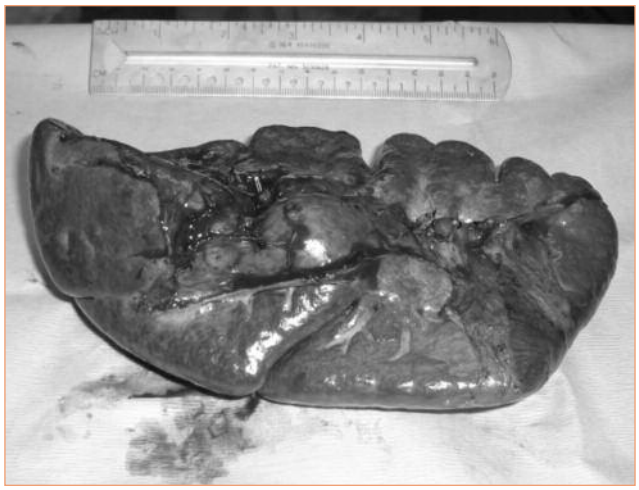

Figure 5. Posterior View of the Spleen After Excision
Weight was approximately 600 g. A normal spleen in a child in this age group typically weighs about 50 g.

monitoring via a rectal probe were standard for all cases. On occasion a 22-gauge or 20-gauge femoral intra-arterial catheter (A-line) was used for both intraoperative and postoperative evaluation of physiologic status.

With the patient anesthetized, the final round of laboratory tests was drawn to determine the current hemoglobin amount, hematocrit, and platelets and the possible need for packed red blood cells or whole-blood transfusion. Once the patient's laboratory findings were within acceptable parameters (hemoglobin > 6 g/dL and platelets > 100/mm^2), the surgery was initiated. Metoclopramide, rectal acetaminophen (30 to 40 mg/kg), and antibiotics helped reduce the chance of febrile response, infection, and akinesis of the bowel.

The surgical approach was through a left subcostal incision (Figures 3 and 4) and had multiple stimulation points for vagal responses from the peritoneum and ligation and suturing of splenic vessels. Most cases were uncomplicated, with fluid replacement being a slow infusion of blood and anesthesia ranging from 1 to 1.3 minimum alveolar concentration of sevoflurane.

The spleen was removed, and the nasogastric tube position was confirmed manually by the surgeon. The mean spleen weight was more than 600 g, with a range from 60 to 1,400 g (Figure 5). Before fascia closure, the team initiated nausea and vomiting prophylaxis as well as pain control measures. Pain control measures also included hindering inflammatory responses with the use of ketorolac in patients who were greater than 3 years of age and had stable platelet counts.

Through repetition of the procedure, a splenectomy protocol was developed and utilized with great success. All of the children were discharged to their families around day 3.

Results

Figure 6 shows a typical postoperative case demonstrating marked overall improvement. Follow-up visits revealed that families were very satisfied with the outcomes of anesthesia, and most of the children either reduced or eliminated their dependency on blood transfusions.

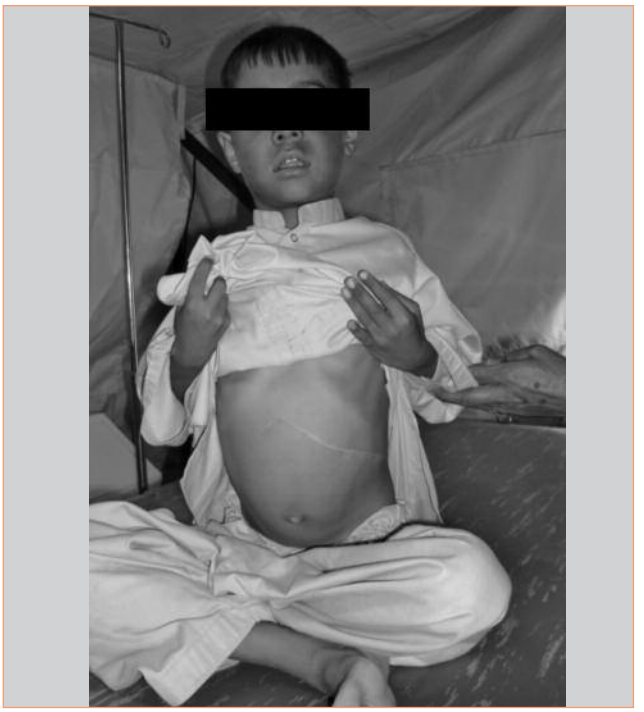

Figure 6. This 6-Year-Old Boy Returned for an Evaluation About 4 Weeks' Postoperatively, Demonstrating Marked Overall Improvement.

Long-term postoperative mean hemoglobin and hematocrit measurements improved, respectively, from 5.4 g/dL and 16.5% preoperatively to 8.7 g/dL and 26.3% postoperatively. Platelet counts improved, ranging from 245,000/mm^3 to nearly 400,000/mm^3 in some cases. Many patients were prescribed aspirin therapy postoperatively due to thrombocytosis.

The most dramatic result was the diminishment in transfusion days. Some children were so severely anemic preoperatively that they needed to undergo transfusion every few weeks. Days between transfusions rose from a mean of 24 days for presurgical treatment to nearly 50 days after splenectomy, with a few cases ranging up to 86 days between transfusions.

Complications did arise during the preoperative, intraoperative, and postoperative courses for some patients. Over the caseload of nearly 45 cases, 1 patient experienced persistent postoperative respiratory distress due to viral pneumonitis, mandating an air evacuation to the large theater hospital. Two patients died during the preoperative evaluation due to complications of the disease. One patient had an acute hemolytic blood transfusion reaction despite our following strict guidelines in the administration of blood products and whole-blood donations. This may have occurred because of the frequency

of transfusions the child had experienced in the past or because of some other acute process. The other case of morbidity was due to severe congestive heart failure after blood transfusion.

Discussion

There are many ways to perform these procedures and render a safe patient outcome. To help prevent further incidents of congestive heart failure and overload, we developed a novel technique of using ultrasonography to image heart function before surgery to assess for left ventricular contractility. Chest radiographs were also useful to determine the patient's risk of congestive heart failure.

All patients were categorized as ASA physical status III or IV, and overall morbidity and mortality were low for these high-risk procedures. The most frequent postoperative morbidity was prolonged stay in the intensive care unit due to ileus. The second most common morbidity was blood transfusion reactions. These patients had multiple exposures to blood products, increasing their risk to transfusion reactions. Only surgical treatment of hypersplenism due to TM was considered for this pediatric patient population due to limited access to other treatment modalities as described earlier. Chelation therapy and bone marrow transplantation are not available in the third-world and developing countries. Transportation of local Afghan nationals out of theater to Western countries was rarely approved and was usually reserved only for the high-profile cases. Other issues related to the surgical care for these patients included consuming limited resources such as blood and inpatient space. Frequently, balances were struck to include partnerships with provincial hospitals to minimize total inpatient days spent at the US hospital. All of these controversies were discussed in an interdisciplinary fashion preoperatively to include anesthesia, nursing, medicine, interpreters, and family members. Some hospital team members had reservations about participating in these high-risk procedures in an austere environment and were allowed to be excluded from participation.

Although a surgical cure was never the goal, overall these patients experienced a better quality of life postoperatively, as transfusion requirements dramatically diminished and their nutritional status improved. Hemoglobin level and hematocrit as well as platelet counts all improved in the postoperative period. Mean days between transfusions nearly doubled after splenectomy. The overall reduction of transfusions with increased quality of life was often reported at the postsurgical follow-up visit. Parents expressed gratitude through the interpreters that their child would now work and play with their brothers and sisters.

These types of cases help to boost the morale of the hospital staff and improved relations with the local national Afghans. This winning of the "hearts and minds" of the civilian population had beneficial operational effects as well. Frequently, cooperation in surrounding communities increased as a result of the humanitarian care provided to children from these villages. Overall, these cases were extremely challenging both from the surgical and anesthetic management perspective; however, the successes were many and complications were relatively low.

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