Recent Progress in Organ Transplantation

Etsuro Motoyama, M.D.
Professor of Anesthesiology
University of Pittsburgh
School of Medicine

INTRODUCTION

Although my lecture is entitled "Recent progress in organ transplantation," I will limit my remarks solely to liver transplantation because of the special interest in this subject in Japan.

The first human orthotopic liver transplantation was performed in 1963 and relatively long-term survival was achieved in 1967 with the use of azathioprine, an immunosuppressant that inhibits the proliferation of both T- and B-lymphocytes. The long-term survival rates, however, remained well below 50% until the early 1980s because of technical difficulties, inexperience in perioperative care, and organ rejection (1,2).

The discovery of cyclosporine, an antibiotic and T-lymphocyte suppressor, and its wide clinical use in the early 1980s virtually revolutionized organ transplantation in North America and Europe. The five-year survival rate of liver transplant recipients increased from less than 30% before cyclosporine to well over 70% (3). In the United States, liver transplantation was endorsed, at a Consensus Development Conference of the National Institutes of Health, as a bona fide therapy for patients with end-stage liver disease, whose mortality rate without transplantation ranged from 50% to 80% (4).

FK506, a new antibiotic immunosuppressant that was developed in Japan and is currently under clinical trials, is much more potent and has a higher immunospecificity and lower toxicity than cyclosporine. Early trials have shown further improvements in graft and recipient survival as well as in the quality of life after liver transplantation.

EPIDEMIOLOGY

Currently in the United States more than 70 transplant centers perform approximately 2000 liver transplantations annually, about 350 of which are performed in children.
mostly less than six years of age. Similar numbers of liver transplantations are performed in Europe. The number of patients needing donor livers is estimated at about 4000 to 5000 in the U.S. population of 250 million people (5). Although the organization for organ procurement has improved over the last decade, too few donors are available. The nation-wide United Network for Organ Sharing (UNOS) program continues efforts to increase donation, and since 1987 hospitals have been required by law to identify potential organ donors and to ask their family members for organ donation.

According to recent UNOS statistics, the major causes of brain death in organ donors are: motor vehicle accident (30%), cerebrovascular disease (26%), gunshot or stab wounds (17%), and head trauma (14%).

INDICATIONS AND CONTRAINDICATIONS

Indications and contraindications for liver transplantation are still evolving and are based on factors including the development of skills and technology, donor organ availability, and morbidity/mortality data in patients with end-stage liver disease of various origins. Liver transplantation is indicated for patients with non-malignant end-stage liver disease that will not recur in the engrafted liver. Patients with primary neoplasm confined to the liver are also included.

Common causes of end-stage liver disease requiring liver transplantation in adults include: cirrhosis (postnecrotic, biliary, and alcoholic), sclerosing cholangitis, and acute hepatic failure. In children, biliary atresia and inborn errors of metabolism are most common (3).

Absolute contraindications to liver transplantation include sepsis, acquired immunodeficiency syndrome (AIDS), advanced cardiopulmonary disease, and malignancies not confined to the liver. Relative contraindications may include renal failure, portal or other major systemic vein thrombosis, prior portocaval shunt, cholangiocarcinoma, positive serology for hepatitis B or human immunodeficiency virus (HIV), chronic alcoholism, and advanced age.

Transplantation in the presence of certain diseases is controversial. Transplantation for liver failure from the hepatitis B virus may have a short-term benefit, but the infection usually spreads to the donor organ within a year, and is thus now considered contraindicated. Xenotransplantation using primates (baboon) or genetically engineered animals may solve this problem in the future because human hepatitis does not occur in xenoplanted livers. Transplantation in patients infected with HIV but without the symptoms of AIDS has been performed, but it remains controversial (6).
Since end-stage liver disease generally involves several organ systems, the anesthesiologist must perform a careful review of the history and examination of the patient's physical status and discuss the strategy for perioperative management with the hepatologist and the surgeon (4,5).

Central Nervous System: Hepatic encephalopathy is associated with increased blood levels of a number of chemicals including ammonia, short-chain fatty acids, mercaptans, and false neurotransmitters. Electroencephalography, evoked potential studies, and computed tomography (CT) scans are usually performed preoperatively to rule out the presence of organic disease. Patients with fulminant hepatitis may have cerebral edema with diminished or increased cerebral perfusion. In these patients, perioperative monitoring of intracranial pressure, cerebral blood flow, and metabolism is recommended (7).

Cardiovascular System: A hyperdynamic circulatory state with low vascular resistance may be present resulting from intrapulmonary and mediastinal arteriovenous fistulas and endogenous vasodilators. Resting ventricular function may be normal, but myocardial contractility may be decreased in some patients with liver failure. Echocardiography is performed to rule out myocardial disease in these patients. Left ventricular ejection fraction less than 50% is considered to increase the anesthetic risk (7).

Respiratory System: Breathing is frequently impaired by ascites, pleural effusion and resulting atelectasis. Pulmonary parenchymal abnormalities must be identified preoperatively by means of radiologic examinations and pulmonary function tests, although the presence of ascites and pleural effusion makes pulmonary status difficult to evaluate. Pulmonary infection should be treated appropriately before surgery. Arterial oxygen tension and saturation, monitored by pulse oximetry, may be reduced by intrapulmonary right-to-left shunting (hepatopulmonary syndrome) or atelectasis and ventilation/perfusion mismatch. Oxygen desaturation may improve dramatically after liver transplantation.

Digestive System: Esophageal varices are a common complication of hepatic failure and portal hypertension. Gastric emptying is often delayed, and peptic ulcer is not uncommon, all of which affect the induction and anesthetic management of these patients. Hepatic dysfunction alters absorption, protein binding, and metabolism of drugs, making their pharmacologic effects inconsistent.

Hematologic System: Anemia is common from malabsorption, hypersplenism, variceal bleeding or reduced survival of erythrocytes. The level of coagulation factors other than fibrinogen and factor VIII are often decreased. Thrombocytopenia is seen frequently, and platelet function may be impaired. A complete coagulation profile should be
obtained, and specific coagulation disorders should be treated preoperatively. Serologic tests for hepatitis (A, B, C, D) and HIV are done routinely for the safety of the health care workers in the operating room and intensive care unit.

Renal System: Renal function is often impaired by either hepatorenal syndrome or pre-renal azotemia. Renal function tests, therefore, are essential before liver transplantation. Preoperative hemodialysis or peritoneal dialysis may be required. It is important that the serum potassium level is normal or slightly below normal, because hyperkalemia often develops in the early neohepatic phase of the transplantation when the engrafted liver is reperfused.

SURGICAL CONSIDERATIONS

The successful outcome of this complicated, prolonged, and often stressful procedure depends on close team work between the surgeon and the anesthesiologist. The anesthesiologist must have a full understanding of the surgical procedure and approach, which may change during the course of the operation. Similarly, the surgeon must communicate with the anesthesiologist so that he or she may anticipate the course of surgery and the changes occurring in hemodynamic and other physiologic functions throughout the procedure (5,7).

Donor Liver Preservation

The donor liver is perfused with ice-chilled organ preservative solution in situ before it is removed from the donor's abdominal cavity, then suspended in ice-cold preservative solution without perfusion. Until the late 1980s Collins' solution provided clinically satisfactory hypothermic preservation (cold ischemia time) of the donor liver for up to eight hours. More recently, the University of Wisconsin (UW, or Belzer) solution was shown to extend the cold ischemia time to 18 to 24 hours (8) and has made possible never and more time-consuming approaches, such as transplantation with split or reduced-size livers. Prolonged cold ischemia time has also allowed the anesthesiologist more time for a more thorough preparation of the patient before the induction of anesthesia.

Surgical Procedure

In orthotopic liver transplantation, the most commonly performed procedure, the diseased liver is removed through a wide abdominal incision and replaced with the donor liver in the same location. The procedure can be divided into three stages for the convenience of discussion: the preanhepatic, anhepatic, and neohepatic stages (5,7).

The preanhepatic stage extends from the bilateral subcostal skin incision with a midline extension to the xyphoid process to dissection of all major hepatic vessels, immediately before the ligation and division of the portal vein and hepatic artery. During this stage considerable blood may be lost because of difficult exposure of hilar blood vessels, engorged collateral blood vessels as the
result of portal hypertension, and, in the case of young children with biliary atresia, adhesions from previous surgical intervention (Choledoco-jejunostomy or Kasai's procedure). Considerable hemodynamic instability is not uncommon, due to the compression of the major blood vessels as well as to hypovolemia (9).

The anhepatic stage begins with heptatectomy and ends with reanastomosis of the inferior vena cava (IVC), portal vein, and hepatic artery. Cross-clamping of the IVC during this stage reduces cardiac output by as much as 50% and causes infrahepatic venous stasis, third space fluid loss, and visceral edema resulting in hemodynamic instability (7). In the last ten years, the venovenous bypass technique has been used successfully to reduce hemodynamic instability and morbidity and mortality. The venovenous bypass is instituted without systemic heparinization by cannulating the portal vein and IVC through the saphenofemoral junction and returning blood to the right heart via the right axillary vein using a centrifugal pump (Figure 1). The bypass flow is maintained at about 40% of cardiac output (10). One major limitation of the venovenous bypass technique is that blood flow through the centrifugal pump,
Recent Progress in Organ Transplantation 373

Figure 2. Biliary reconstruction following orthotopic liver transplantation. Biliary drainage can be accomplished via a Roux-en-Y (choledochojejunostomy) or “duct-to-duct” anastomosis (insert). (Reprinted with permission from Starzl TE, Demetris AJ, van Thiel DH: Liver transplantation. N Engl J Med 321: 1014, 1092, 1089.)

with the currently available technology, must be maintained at or above 1 liter per minute to prevent coagulation in the circuit. Thus, the bypass system cannot be used safely in pediatric transplant recipients weighing less than about 20 kg. Fortunately, pediatric patients, especially infants, seem to tolerate cross-clamping of the suprahepatic IVC better than adults provided that adequate circulatory blood volume is maintained.

More recently, a technique of hepatectomy has been developed where the liver is peeled off the IVC without cross-clamping, while systemic venous return is maintained unimpeded. Reconstruction consists of anastomosis of the portal veins, the donor's IVC to the recipient's reconstructed hepatic veins, and of the donor's hepatic artery (often with a portion of the aorta) to the recipient's hepatic artery or the aorta (piggyback technique). Although this technique is time consuming and technically more difficult, with potentially more blood loss, it has been successful, especially in infants and young children, in whom venovenous bypass is not applicable (5).

The neohepatic stage begins with reperfusion of the engrafted liver by unclamping the portal vein, infrahepatic IVC, and suprahepatic IVC. Unclamping of the portal vein
and infrahepatic IVC causes an acute decrease in preload to the right heart. Unclamping of the suprahepatic IVC causes a transient increase in preload and systemic pressure, frequently followed by hypotension and characteristic hemodynamic changes called the "postreperfusion syndrome" (11). The syndrome is characterized by progressive bradycardia, systemic vasodilation, and hypotension and, in severer cases, shock. It appears to be related to the release of yet unknown vasoactive substance(s) from the grafted liver. After reanastomosis of the IVCs and hepatic arteries, biliary reconstruction follows with duct-to-duct anastomosis over a T-tube stent (choledochocholedochostomy). In patients with absent or inadequate biliary duct due to biliary atresia, biliary cirrhosis, or other causes, choledochojejunostomy to a Roux-en-Y limb may be performed (Figure 2). Closure of the abdominal cavity is preceded by meticulous hemostasis and irrigation with saline solution containing antibiotics.

Split Liver, Reduced-size Liver, and Living-related Liver Transplantation

As the result of an organ shortage, especially in children, together with the advent of longer cold ischemic time with the UW solution, three procedures have been introduced to circumvent the need for appropriate-size donor livers (12-14). In the split-liver technique, the liver is divided into the left and right lobes with the concomitant hepatic arteries, portal veins, and biliary ducts, and they are transplanted to two different patients. Reduced-size liver transplantation involves reduction of an organ to an appropriate size for a single recipient. The third, and more controversial procedure, at least in North America and Europe, uses a partial organ from a living related donor. The donor, usually a parent, undergoes a resection of the left hepatic lobe for transplantation to a child, as in living-related kidney transplantation. In Japan, the situation is very different because the concept of brain death is not yet legally established, and living related donors are the only acceptable source of donor organs for liver transplantation. My understanding is that living-related liver transplants, although relatively small in number, so far have succeeded without major morbidity or mortality to the donor parents.

The wisdom of all these procedures has been questioned. Graft survival of reduced-size livers or split livers is only 50%, considerably less than that of whole organs (70% to 80%). Perioperative bleeding (33%) and biliary complications (27%) are also increased. Furthermore, the ischemic time for reduced or split livers is longer, as the resection and biliary ligation must be performed before transplantation (15).

ANESTHETIC MANAGEMENT

Preanesthetic Preparations
The anesthesiologist must carefully discuss the plans
for surgical and anesthetic management of each patient with
the surgeon and other patient care team members long before
the induction of anesthesia. Because of the likelihood of
massive blood loss and hemodynamic, respiratory,
 hematologic, and electrolyte instability intraoperatively, a
system for continuous monitoring of vital signs and rapid
 assessment of blood gas tensions, acid-base status,
 electrolyte, serum ionized calcium, and blood glucose should
be at hand.

Premedication is not routinely given to liver
transplant recipients because of possible hepatic
encephalopathy, full stomach, and hematoma formation
following intramuscular injection. Since most recipients
have a positive psychological outlook toward the surgery,
 thorough preoperative counseling usually suffices for
preoperative preparation and allows the alert patient to
interact with family members before surgery (7).

Induction and Maintenance of Anesthesia
Patients for liver transplantation often have eaten
shortly before being called into the hospital for surgery.
In addition, emptying of the stomach is delayed in patients
with liver disease. Induction of anesthesia, therefore, is
often accomplished by means of rapid-sequence technique with
preoxygenation and cricoid pressure (Sellick maneuver). A
small dose of fentanyl (2-3 µg/kg) or a sedative (midazolam,
50-100 µg/kg) may be used intravenously for sedation before
the induction. Induction and intubation are usually
achieved with thiopental (4 mg/kg) and succinylcholine (1-2
mg/kg) preceded by a small dose of non-depolarizing muscle
relaxant to prevent fasciculation. Ketamine (2 mg/kg) or
etomidate (0.3-0.5 mg/kg) have also been used for induction,
especially in patients with hemodynamic instability.

After proper positioning of the endotracheal tube is
confirmed by means of bilateral chest auscultation and the
tube well secured, mechanical ventilation is instituted with
oxygen and nitrogen. Nitrous oxide is usually not used
because it causes intestinal distension, increases the size
and risk of air emboli, and depresses the myocardium.

The recipient is placed on a well-padded operating
table covered with a warming blanket, with both arms
outstretched and resting on well-padded arm boards. A large
intravenous catheter (7.5 French or larger) is placed in the
right antecubital or axillary vein and another large-bore
catheter is placed in the left external or internal jugular
vein for rapid infusion systems. In children, four large
intravenous catheters (14 to 18 gauge) are inserted in the
upper extremities. An 18-gauge arterial cannula is inserted
into the femoral artery, and a 20-gauge catheter is inserted
in the right radial artery (after Allen's test) for a back
up, for continuous monitoring of arterial pressure and blood
gas sampling. A balloon-tipped pulmonary artery catheter is
placed through the right internal jugular vein (5,7).

Electrocardiograph electrodes are secured, and an
indwelling urinary catheter attached to a continual
measuring device, esophageal and rectal thermister probes, an esophageal stethoscope, and a nasogastric tube are inserted. The head and exposed upper extremities are wrapped with vinyl covers to prevent heat loss, a precaution most important in small children. The occiput, knees, and ankles are placed on padded sponges, and the body is so positioned to prevent any pressure injury during the prolonged period of surgery and anesthesia, which on average lasts 12 hours or longer (5).

Maintenance of Anesthesia

Anesthesia is maintained primarily with narcotics (fentanyl or morphine), hypnotics (midazolam), and supplemental inhaled anesthetics. Isoflurane is most commonly used, because it maintains hepatic blood flow and causes no hepatotoxicity. The procedure requires prolonged and profound muscle relaxation, which pancuronium usually provides.

Intraoperative medications include antibiotics repeated every 4 to 6 hours, depending on the particular drugs, a large dose of corticosteroid (methylprednisolone, 1 g) and cyclosporine or FK506 after reperfusion of the donor liver. Additional medications may include a small dose of dopamine (2-3 μg/kg/min) to maintain renal blood flow and urinary output, especially in small children without venovenous bypass during the anhepatic stage. Sodium bicarbonate may be given as needed for metabolic acidosis during and after the anhepatic stage.

Massive blood loss, amounting as much as 500 ml per minute at times, is not uncommon during liver transplantation. In both adults and children, the equivalent of more than 20 blood volumes has been lost during liver transplantation (16), although, with more experience and improved techniques, the blood loss has decreased somewhat. To meet the need for rapid transfusion during liver transplantation, a rapid infusion system was developed (17) that can deliver prewarmed, premixed blood with controllable rapid rates up to 1.5 liter per minute (Figure 3). In addition, an autotransfusion system salvages up to 40% of red blood cell loss, thereby reducing the need for banked blood. When anticoagulated with citrate solution, washed with balanced salt solution, centrifuged, and autotransfused back to the patient, scavenged blood produces satisfactory coagulation and electrolyte balance with minimal increase in plasma free hemoglobin (7). Bacterial contamination can occur but is quantitatively negligible. Autotransfusion is contraindicated in patients with intraperitoneal infection or abdominal neoplasm.

Blood volume is maintained with relatively low hematocrit (25% to 28%) to reduce red blood cell loss. Fluid deficit is replaced with crystalloids without dextrose, because hyperglycemia is common with a non-functioning or absent liver. Plasma oncotic pressure is often decreased in patients with end-stage liver disease, requiring blood volume replacement with colloid solutions (albumine, plasma proteins, or fresh frozen plasma).
Major blood loss combined with hepatic failure can produce severe coagulopathy during liver transplantation. Assessment of the coagulation profile, however, does not yield results quickly enough. Thromboelastography is an extremely useful alternative for guiding coagulation therapy during liver transplantation (18). The technique consists of a tiny cup containing whole blood and a tiny rod suspended from a transducer that is lowered into the blood specimen at body temperature (19). As fibrin strands form on the surface of the rotating rod, an increase in shear elasticity is recorded on a strip chart recorder. Thus, thromboelastography monitors coagulability of whole blood, rather than the quantity of coagulation factors, and assesses the entire process of coagulation and fibrinolysis. Clinically useful information can be obtained within 30 minutes (20).

Hypothermia is a real problem during liver transplantation because of prolonged exposure and evaporative heat loss, especially in small children. All infusants and irrigation fluids should be prewarmed to body temperature to minimize heat loss. Whenever possible,
Exposed abdominal viscera should be covered with sterile vinyl sheets to minimize evaporative heat loss and prevent hypothermia and resultant cardiovascular instability.

Once the allograft starts to function, hemodynamic and metabolic stability is gradually restored. The need for inotropic support usually diminishes, and urine output starts to increase even in patients with hepatorenal syndrome (4). Metabolic function of the engrafted liver is often detectable within two hours after reperfusion. Lactate, citrate, and blood glucose levels start to decrease and coagulopathy improves. The anesthesiologist often notices dramatic changes in the rate of metabolism of pancuronium, a sign of hepatic function.

At the conclusion of surgery, the recipient is transported to the intensive care unit (ICU) deeply sedated with narcotics and without reversal of muscle relaxants. The electrocardiogram, heart rate, blood pressure, and oxygen saturation with pulse oximetry are monitored in transit to the ICU while the ventilation is maintained manually with an appropriate level of positive end-expiratory pressure (5-15 cmH₂O). Upon arrival at the ICU, monitoring of all hemodynamic indices and mechanical ventilation are resumed.

**POSTOPERATIVE MANAGEMENT**

The recipient is allowed to recover from anesthesia and muscle relaxation in the ICU. The immediate postoperative care is similar to that after other major surgical procedures. When the engrafted liver is functioning well, lactate and citrate accumulated from transfused blood continue to be metabolized, resulting in systemic metabolic alkalosis. Hypertension may result from cyclosporine, inadequate sedation and analgesia, or hypervolemia. Meticulous postoperative pulmonary care is essential before the recipients can be weaned from mechanical ventilation. Most patients who were not ventilator dependent preoperatively and who have no major complications are extubated within 24-48 hours from the end of surgery and anesthesia. The postoperative care of patients following liver transplantation has been reviewed (10).

An immunosuppression regimen consisting of cyclosporine or FK506, azathioprine, and prednisone is started shortly after transplantation. Primary non-function of the allograft has become less frequent since organ preservation has improved with the use of the UW solution. Organ rejection, however, is still not uncommon. Immunosuppressive therapy for organ transplantation has been reviewed extensively (21,22). Other complications include vascular and biliary anastomosis leaks, thrombosis of the hepatic artery, especially in infants and young children, and abdominal abscess (23).

As in the recipients of other organ transplants, lymphoproliferative disease (LPD) is the most life-threatening complication of long-term immunosuppressive
therapy. Patients receiving liver transplants have an estimated incidence of 1% to 3% as compared with 5% to 13% in recipients of heart or heart-lung transplants. Epstein-Barr virus is confirmed in more than 85% of adult and 50% of pediatric patients (24). The time to presentation of LPD varies from 1 to 150 months after transplantation (15). According to recent statistics from UNOS, the major causes of death among liver transplant recipients are infection (37%), graft failure (15%), cardiovascular disease (12.3%), hemorrhage (8.6%), and LPD (7.3%).

REFERENCES


