Anesthetic Management in Pediatric Liver Transplantation

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An increasing number of pediatric patients undergo liver transplantation, and it has become an effective and definitive treatment of choice for pediatric end-stage liver disease patients. However, liver transplantation in pediatric patients differs greatly from that in older individuals with respect to not only surgical techniques, immunosuppression, and post-operative managements, but also to intraoperative anesthetic management. The present review provides an overview of the current development and clinical practices in anesthetic management of pediatric liver transplantation.

Key Words: Liver transplantation, Child, Anesthesia
중심 단어: 간이식, 소아, 마취

INTRODUCTION

Since the early 1990s, liver transplantation has been the treatment of choice in patients with end-stage liver disease (ESLD). Due to the growing success of liver transplantation, a rapidly increasing number of pediatric patients are being placed on wait lists for transplantation, which produces a significant gap between supply and demand for size-matched organ donation. Innovative surgical techniques, such as split liver and reduced liver grafts, can be effective ways to manage a limited donor pool. However, the number of pediatric patients waiting for transplantation has been rapidly increasing despite the limited but consistent number of cadaveric donors. Despite advances in the development and treatment of pediatric ESLD, a shortage of available organs continues, and more severely deteriorated patients continue to be enrolled as liver transplantation candidates, thereby increasing perioperative morbidity and mortality rates due to conditions such as portopulmonary hypertension or hepatorenal syndrome.

INDICATIONS

Among the various surgical indications for liver transplantation in pediatric patients, the most common is biliary atresia, in addition to toxicity, infection, and genetic and metabolic diseases. Liver diseases in pediatric populations exhibit particular characteristics according to age group: neonatal hemochromatosis is prevalent in neonates; extrahepatic biliary atresia occurs in infants; and more heterogeneous disease patterns in older children, such as autoimmune hepatitis, α-1 antitrypsin deficiency, Wilson's disease, and even liver diseases prevalent in adults. However, in 75% of children diagnosed with acute hepatic failure, no definitive etiology can be confirmed(1).

PREOPERATIVE EVALUATION

Meticulous preoperative evaluation, including detailed medical history and physical examination, which focus on

the etiology of hepatic failure and reasons for liver transplantation, must be performed. Although pediatric patients scheduled for liver transplantation exhibit typical signs and symptoms of hepatic failure, such as coagulopathy, ascites, and varices, such characteristic findings can be ruled out in hepatic failure patients with metabolic defects or genetic syndrome. Although the aforementioned hepatic conditions can be present without symptoms of hepatic failure, possible organ dysfunction related to underlying disease should be kept in mind. For example, Alagille syndrome is known to be accompanied by congenital heart disease, which requires additional cardiac catheterization for detailed evaluation of pulmonary hypertension and right ventricular function. Hyperoxaluria is often accompanied by hypertension, renal failure, and heart failure. Patients with α-1-antitrypsin deficiency or cystic fibrosis are likely to exhibit pulmonary disease. Patients with hemochromatosis also exhibit diabetes, cardiomyopathy, and anemia.

In addition to thorough preoperative evaluation, detailed explanation and discussion regarding the risks and benefits of transplantation should be held with the patient's guardians before surgery. Because liver transplantation can be a high-risk surgery, rigorous discussion about perioperative morbidity and mortality, hemorrhage, massive transfusion, neurological, cardiovascular and respiratory complications, postoperative ventilator care, intensive care unit management, and finally, the possibility of reoperation, should all be considered.

Blood tests for coagulation status, such as partial thrombin time (PT), aPTT, fibrinogen level, platelet count, acid-base status, electrolyte and glucose levels, and hepatic and kidney function should all be examined. Cardiac imaging studies, such as transthoracic echocardiography, should be performed to examine patient cardiac function. Furthermore, typical findings for the presence of portal hypertension, such as esophageal varices and ascites, and previous history of surgery or procedures and/or other comorbidities that may affect anesthesia should be examined.

INDUCTION AND MAINTENANCE OF ANESTHESIA

Anesthetic induction should be thoroughly individualized based on hepatic disease etiology, related cardiac conditions, hemodynamic instability, electrolyte abnormalities, amount of ascites, and history of gastrointestinal bleeding due to gastric varices. Anesthetic induction can be performed using either a sevoflurane mask or intravenously. Sevoflurane mask induction can be implemented in small children with no intravenous (IV) access and those with a small amount of ascites, and thus, lowering the risk for vomiting or aspiration. If patients already have IV access, anesthetic induction via IV anesthetics can be safe. The anesthetics can be selected from among propofol, ketamine, and etomidate, based on the patient's hemodynamic status.

Although isoflurane is the recommended anesthetic because it can conserve splanchnic blood flow and vasodilate the hepatic vasculature, and therefore, improve organ perfusion, other choices of anesthetics, such as sevoflurane or desflurane, are preferred(2,3). For the choices of muscle relaxant, succinylcholine can be used in case of rapid sequence induction. However, due to the risk for hyperkalemia, high-dose rocuronium may be preferred. Cisatracurium can be used for continuous infusion during surgery because it can be metabolized independently of hepatic function. Most pediatric patients are intubated during surgery using cuffed endotracheal tubes, even for small infants, with proven safety(4).

Continuous infusion of opioid can be used for additional analgesics during surgery. Fentanyl is preferred due to its subtle effects on hepatic function(5). Sufentanil not only confers 5~10 times stronger analgesic potency compared with fentanyl, it also can be hemodynamically safer even at higher dosages, which makes it a safe analgesic option during liver transplantation surgery(6,7).

Infants and small children are especially vulnerable to hypothermia during the perioperative period due to malnutrition, high cardiac output, peripheral vasodilation, frequent ascites drainage, and hemorrhage. Moreover, the cold temperature of the retrieved organ may aggravate hypothermia during liver transplantation. Therefore, it is important to maintain patients in a normothermic state during liver transplantation to preserve normal physiological status, including normal cardiac function and enzymatic systems such as the coagulation cascade. In pediatric liver transplantation settings, both active and passive warming meas-

ures should be applied to maintain normothermia, even during the preparation period, after anesthetic induction. Patients should be placed on a pressure-relieving warming mattress during central catheterization and other preparation periods, and should be covered by a convective warming system (Bair Hugger, 3M, Minneapolis, MN, USA) (Fig. 1A, B). Mechanical ventilation with heat and moisture exchangers, and high-flow fluid warming devices (Fig. 1C) for IV fluid and blood can all be beneficial for maintaining body temperature.

MONITORING

Hemodynamic parameters in patients should be monitored according to the standard American Society of Anesthesiologists (ASA) guidelines, including arterial blood pressure, central venous pressure, and urine output. Although the routine application of transesophageal echocardiography is not recommended, it can be applied to small children, especially those with underlying congenital heart disease(8).

There has been controversy regarding pulmonary artery catheterization in pediatric patients, with several reports describing life-threatening complications related to catheterization, especially in high-risk children(9-11). Similarly, hemodynamic parameters, such as pulmonary arterial pressure, core temperature, and cardiac output, can be useful in intraoperative hemodynamic monitoring; however, they are not recommended as routine monitoring parameters. In addition,

pulse pressure variability and pleth variability index can be adopted as a dynamic volume index, and transesophageal Doppler can also reflect cardiac output. Several studies have reported the utility of such dynamic parameters and their use has been increasing during transplantation surgery, despite the lack of formal validation.

LINES

To enable rapid transfusion of blood product(s) or IV fluid resuscitation during liver transplantation surgery, it is crucial to obtain >2 large-bore IV access routes in the patient's upper body before surgery. Because the inferior vena cava (IVC) is clamped during the anhepatic phase of the transplantation process, delayed time for drug(s) to reach the central circulation can be expected. Central IV access should be acquired both for central venous pressure (CVP) monitoring and administration of vasoactive drugs. Central venous catheterization can either be placed at the internal jugular or subclavian vein under radiological intervention. According to reports, rapid blood product transfusion via central venous access in children <12 months of age is one of the risk factors for transfusion-associated cardiac arrest, which may be accompanied by hypocalcemia and hyperkalemia(12,13) (Table 1).

Arterial access is highly useful for real-time blood pressure monitoring, and must be recommended during the perioperative period. Among the various arterial access routes,
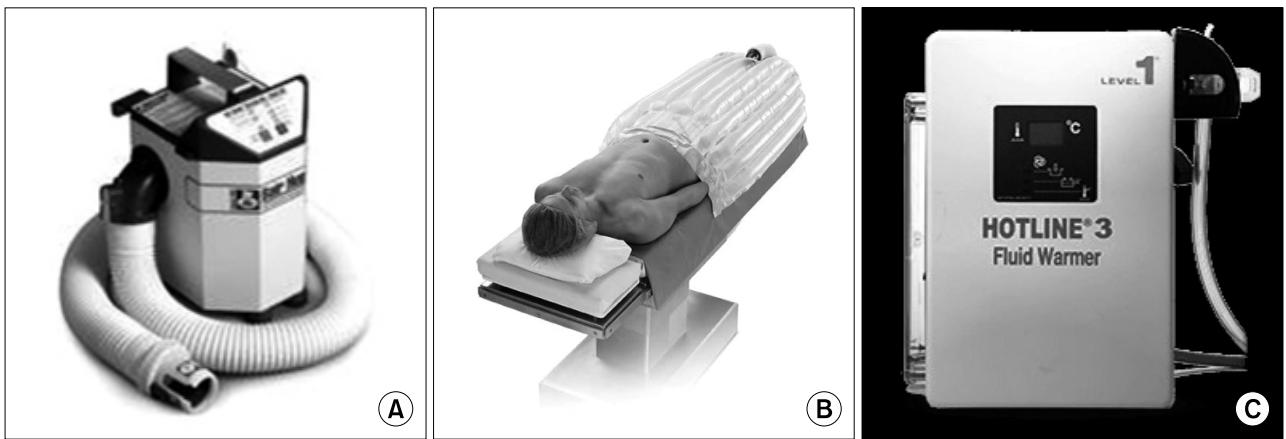

Fig. 1. Patient warming devices. Bair hugger warming unit (A), Bair hugger warming blanket (B), Hotline fluid warming devices for IV fluid and blood (C).

Table 1. Surgical stages and related anesthetic concerns

Surgical stage	Anesthetic concerns
Preanhepatic (dissection)	
Dissection of diseased liver	Large blood loss
	Fluid and blood products resuscitation
Anhepatic	
IVC clamped	Fluid management
	Correction of metabolic abnormalities; hyperkalemia, hypocalcemia, acidosis
Removal of diseased liver	Prepare for reperfusion with adequate volume resuscitation and titration
Reperfusion	Correction of metabolic abnormalities; hyperkalemia, hypocalcemia, acidosis
	Air embolism
Neohepatic	
Hepatic artery anastomosis	Hematocrit maintained <25%
Creation of biliary drainage	Fluid management

Abbreviation: IVC, inferior vena cava.

the radial artery is preferred for its easy accessibility and in cases requiring aortic clamping during the surgical procedure. Although the possibility of limb ischemia and dampened pressure signal during aortic cross clamp can be expected(14), femoral arterial cannulation can be used relatively safely. It is recommended to acquire two arterial lines during surgery due to the likelihood of dampening and the occurrence of mechanical interference during extended operation times, and also for concurrent monitoring of blood pressure during blood sample withdrawal via arterial access.

Although pulmonary artery catheterization can be a useful method to monitor cardiac output because hemodynamic parameters exhibit dynamic changes during liver transplantation, the high risk for related complications has reduced its application. In addition, a urethral catheter and nasogastric tube should be placed during surgery. Endotracheal tubes, and all monitoring cables and catheters need to be organized while devoting attention to patient position to facilitate access by anesthesiologists during surgery.

INTRAOPERATIVE MANAGEMENT

1. Pre-anhepatic phase

The goal of anesthetic management during the pre-anhepatic phase is to maintain hemodynamic stability, to avoid acidosis and electrolyte imbalance, and to maintain normothermia and normoglycemia. A massive amount of bleeding and hypotension can occur during the pre-anhepatic phase(15), especially in patients who have undergone previous abdominal surgery, ascites, and damaged synthetic liver function. Transfusion is recommended for hemorrhage; however, overtransfusion should be avoided. Guidelines for transfusion during liver transplantation surgery can vary among different institutions and anesthesiologists(16). However, most importantly, clinical decisions should be made based on close communication between the surgical team and anesthesiologists during the perioperative period. Intraoperative hypotension can be accompanied by massive hemorrhage, ascites drainage, and acidosis; therefore, colloid (e.g., 5% albumin) infusion can also be considered to preserve intravascular volume, with additional vasopressor infusion also in consideration.

The most common cause of hypotension during liver transplantation is hypovolemia. CVP and urine output are commonly used parameters for monitoring intravascular volume. However, changes in intra-abdominal pressure during surgery may be misleading in accurately monitoring CVP. Close communication between the surgeon and anesthesiologist can be very important in evaluating the patient and the graft, as much as changes in CVP and, thus, should aim for as much guidance as possible in proper fluid therapy during surgery.

2. Anhepatic phase

Clamping of the IVC, either totally or partial cross clamping, during the anhepatic phase reduces the preload that causes hypotension. Dramatic decreases in blood pressure can be expected in pediatric patients awaiting liver transplantation due to metabolic disease and hepatoblastoma because this patient population has less developed venous collateral with less portal hypertension due to relatively normal hepatic function. Acidosis, aggravating hyperkalemia, and interruption of gluconeogenesis leads to hypoglycemia.

Patient body temperature continues to drop during anastomosis with cold-graft organs placed in the abdominal cavity. The anesthetic goal during this phase of the surgery is to maintain hemodynamic stability through adequate intravascular volume and to maintain normoglycemia, normothermia, and normal acid-base and electrolyte balance. The accumulation of lactic acid causes rapid drops in serum pH; therefore, close monitoring is needed.

Hypotension during the anhepatic phase occurs from a marked decrease in preload due to clamping of the IVC, which is restored from increasing preload by declamping of the IVC. Therefore, careful administration of vasopressor can be more appropriate than overtransfusion because a large amount of fluid or blood product(s) can cause congestion in the graft. Hence, maintenance of normal CVP level and the target hemoglobin level of 8 g/dL (80 g/L) are recommended(17).

3. Reperfusion

As the graft is being reperfused by consecutively unclamping the vascular anastomosis, the circulatory system of the recipient is being exposed to cold fluid, potassium ions, various ischemic factors, and even venous air emboli from the donor's liver, which all lead to hypotension, malignant ventricular dysrhythmia, and in severe cases, cardiac arrest(18). This hemodynamic change is known as post-reperfusion syndrome(19). Vigorous effort in anticipating and reducing related clinical risk factors is crucial before reperfusion, such as actively treating hyperkalemia during liver transplantation. Insulin therapy, hyperventilation, IV injection of calcium chloride, sodium bicarbonate, and furosemide can all help to lower potassium levels; thus, hyperkalemia should be treated before reperfusion.

The amount of venous return increases as the IVC and portal vein are unclamped; however, increased endogenous mediators cause >30% decrease in mean arterial blood pressure and increased pulmonary vascular resistance. As such, post-reperfusion changes occur conventionally and careful evaluation of fluid status for avoiding overfilling and meticulous use of vasopressors and inotropes are recommended. Patient body temperature drops by >1℃ immediately after reperfusion. IV injection of calcium chloride, lidocaine, sodium bicarbonate, and epinephrine can be prepared before

reperfusion, and be repeatedly applied. To avoid hypotension and hyperkalemia, temporary application of 100% oxygen or reduced use of volatile anesthetics can be recommended. The surgical team should thoroughly wash the donor organ to prevent the influx of high levels of potassium ion, lactate, cell debris, and air into the recipient circulatory system, with slow unclamping of the portal vein during the surgical procedure. Not only vigilance, but also close communication between the surgeons and anesthesiologists, is absolutely necessary during this period of liver transplantation. Anesthesiologists should be able to provide the necessary cardiopulmonary resuscitation or cardiac defibrillation to properly treat life-threatening arrhythmia at any time.

4. Neohepatic phase

Persistent coagulopathy and continuous blood loss from vascular anastomosis and the surface of the partial donor graft have been noted during the neohepatic phase, even after reperfusion. Meticulous fluid management is needed to avoid graft congestion from fluid overload. When direct aortic conduits are necessary for the graft, the aorta needs to be cross-clamped, which causes more serious hemodynamic instability. Unlike adult patients, either roux hepatico-jejunostomy (bile duct to jejunum) or choledocho-choledochostomy are performed in pediatric patients. Once the graft organ begins to function, acid-base status and electrolyte abnormalities begin to recover and oliguria due to hepatorenal syndrome can be resolved.

Another consideration after reperfusion in pediatric liver transplantation is the likelihood of vascular thrombosis, which for pediatric patients can be hypercoagulable after liver transplantation probably due to reduced levels of protein C, protein S, plasminogen, antithrombin III, and increased levels of non-liver related factor VIII(20,21). According to a Cochrane review published in 2009, the incidence of hepatic artery thrombosis after liver transplantation was 2.9% in adults, while 8.3% were reported in pediatric patients, with a mortality rate of up to 25%(22). The risk for hepatic artery thrombosis increases with greater arterial size discrepancy, lower patient weight, reoperation, and longer surgical times. Moreover, higher blood viscosity with higher hematocrit levels increases the risk for

thrombosis. Therefore, setting the target hemoglobin level as low as 8 g/dL (80 g/L) is recommended. PT and aPTT levels should also carefully be monitored to avoid over-correction. Prophylactic use of acetylsalicylic acid (i.e., aspirin), alprostadil (PGE1) and heparin are also available at many institutions(23,24).

Careful monitoring of the effective oxygenation and ventilation during fascia closure toward the end of the surgery can be important. Continuous monitoring of blood loss and hemodynamic stability are also crucial, even during post-surgery transport of the patients to the intensive care unit. Care must be taken to mitigate the risk for tight abdominal closure, especially for small infant recipients or in cases of greater graft organ size, which all carry a higher risk for graft displacement and compression. Staged abdominal closure can be recommended in such cases.

5. Perioperative extubation

Recent reports have described safe and successful extubation in the operating room after liver transplantation in patients with stable hemodynamics, short surgery time, and not much hemorrhage(25,26). In a single-center retrospective analysis involving 84 pediatric patients who were extubated in the operating room after liver transplantation according to standard extubation criteria, 65% of the patients who met the extubation criteria had a lower re-intubation rate and demonstrated a tendency toward shortened ICU and hospital stays. However, patients with possible reoperation, hemodynamic instability, preoperative encephalopathy, airway compromise, and mechanical ventilator dependency were excluded from the extubation candidates. Extubation inside the operating room depends not only on the transplantation center, surgeons, and anesthesiologists, but also on the patients, type of surgery, and graft-related factors. When all related factors are carefully considered, secure extubation can successfully be performed.

6. Early postoperative phase

The therapeutic goals during the early postoperative phase are hemodynamic stability and maintenance of graft function consistent with that of during the intraoperative period. Administration of blood and fluid need to be titrated. Although continuous loss of blood and the need for

transfusion is expected during surgery, maintenance of hematocrit level >25% is avoided due to the risk for thrombosis. Perioperative hypovolemia usually causes decreased urine output; however, sepsis, poor graft function, and poor preoperative renal function are all possible risk factors for early renal dysfunction. Therefore, appropriate maintenance of intravascular filling and cardiac output is needed to improve renal blood flow. However, the presence of pleural effusion, overloaded fluid, and large graft size can deteriorate respiratory mechanics and aggravate respiratory function.

CONCLUSION

Anesthetic management of pediatric liver transplantation should be accompanied by a profound understanding of the physiological and metabolic changes in ESLD, and its implications for physiological and multi-organ dysfunction during the perioperative period. Remarkable changes during each surgical step of liver transplantation should be anticipated and managed. Above all, close communication between the surgical team and the anesthesiologists is the most important issue in patient management.

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