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Anesthetic principles in living-donor liver transplantation at Kyoto University Hospital: experiences of 760 cases

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Introduction

The first living-donor liver transplantation (LDLT) in Japan was conducted in November 1989 at Shimane Medical University Hospital [1]. At Kyoto University Hospital, the procedure was first performed in June 1990, the second attempt in Japan. By the end of 2001, LDLT had been performed on 728 patients (with a total of 760 attempts, including repeated LDLT for some patients) in our hospital. In most of the earlier cases, a child received a liver donated by a parent. Since 2000, however, about 60% of the recipients have been over 15 years of age (Fig. 1). Thus, LDLT has changed from transplantation to children only to transplantation to patients of various age groups, including adults. Along with this change, anesthesia and intraoperative care for LDLT have also changed. Since the Organ Transplantation Act came into force in October 1997, brain-dead donor organ transplantation is now legally possible in Japan. At our hospital, transplantation of livers from brain-dead patients had been performed in 10 patients by 2001. This article will review anesthesia for LDLT conducted at our hospital and discuss the anesthetic principles for such operations in comparison with those from brain-dead donors.

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Preoperative conditions

Table 1 shows the recipients of LDLTs conducted at Kyoto University Hospital divided by age into two groups: the child group (younger than 15 years) and the adult group (age 15 and over). In the child group, bile retention was the leading underlying disease (74%), and biliary atresia was responsible for bile retention in 93% of these patients. In the adult group, the underlying disease necessitating liver transplantation showed more diversity, and included liver cirrhosis, fulminant hepatic failure, metabolic disease, tumors, and primary biliary cirrhosis.

Patients with terminal-stage liver cirrhosis who are indicated for liver transplantation often have esophageal varices, gastrointestinal bleeding, ascites, and pleural effusion due to portal hypertension. In these patients, diuretics are sometimes administered to reduce the ascites and pleural effusion, and, hence, the circulating blood volume before surgery is sometimes lower than normal. Thrombocytopenia due to marked splenomegaly, anemia, or abnormal coagulation is often seen in these patients, and requires preoperative transfusion of a concentrated erythrocyte preparation [red cell concentrate in mannitol-adenocine-phosphate solution (RC-MAP)], and concentrated platelets, or fresh frozen plasma (FFP). When children with biliary atresia have fever that is resistant to antibiotics or other treatment, we consider them to be candidates for surgery if the fever is attributable to ascending cholangitis. Osteoporosis due to disturbed absorption of lipolytic vitamins and resulting in multiple fractures is sometimes seen. In such patients, particular care is needed to avoid fracture when transporting the patients or changing their position. Patients with metabolic disease but without compromised liver function, (e.g., patients with familial amyloidosis) are sometimes indicated for LDLT. Because the level of liver function varies greatly among recipients of LDLT, the anesthesiologist needs

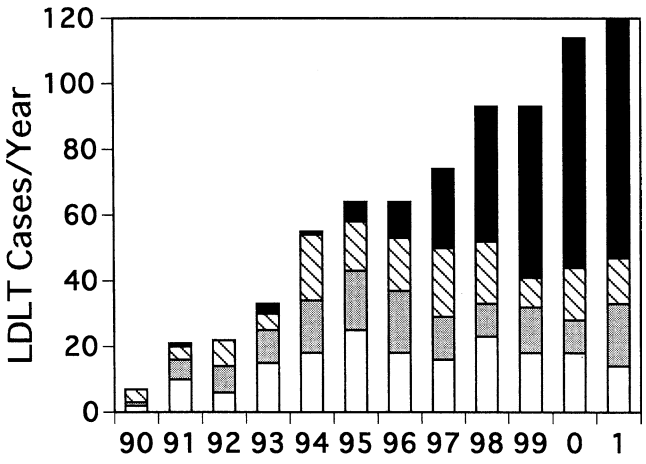

Fig. 1. Annual numbers of patients, by age, who had undergone living-donor liver transplantation (*LDLT*) at Kyoto University Hospital by the end of 2001. *Black bars*, Under 15 years of age; *striped bars*, 5–15 years; *gray bars*, 1–5 years; white bars, under 1 year of age

Table 1. Underlying diseases of patients, grouped by age (younger than 15 years and 15 years and over), who had undergone liver transplantation at Kyoto University Hospital by the end of 2001

	<15 Years	≧15 Years
Cholestatic diseases	356	46
Cirrhosis	20	56
Fulminant hepatic failure	27	40
Metabolic disorders of the liver	39	20
Hepatic tumor	12	47
Failure of primary graft	20	14
Autoimmune hepatitis	1	7
Primary biliary cirrhosis	0	30
Primary sclerosing cholangitis	2	16
Others	2	5

to have adequate information about the patient's preoperative condition, especially regarding coagulation, platelet count, risk of bleeding from esophageal varices, degree of collateral circulation development, presence or absence of hepatic encephalopathy, and the severity of intraperitoneal adhesions due to past operations.

It is worth noting that 17 patients had marked pulmonary shunt, accompanied by hypoxemia due to hepatopulmonary syndrome. One of the 16 patients who underwent LDLT for Alagille's syndrome (a paucity of intrahepatic bile ducts, often accompanied by cardiovascular malformation such as peripheral pulmonary artery stenosis) had severe stenosis of the aortic valve (pressure gradient of 88 mmHg). This patient underwent prophylactic intraaortic balloon pumping (IABP) treatment during the perioperative period [2]. Some children complicated by tetralogy of Fallot or double-outlet right ventricle also underwent LDLT. In these patients, radical surgery for cardiac malformation was performed in advance in view of the risk of paradoxical embolism during LDLT.

In most instances, hepatic encephalopathy was the outcome of exacerbation of fulminant hepatic failure or chronic hepatitis. These patients required preoperative hemopurification by means of plasma exchange, exchange transfusion, continuous hemodiafiltration, etc., and 72% of all patients with fulminant hepatic failure (48/67) were preoperatively managed in the intensive care unit (ICU). Some of them had undergone mechanical ventilation before referral to our hospital or required tracheal incubation in the ICU before LDLT. Of the 67 LDLTs performed for fulminant hepatic failure, 58 (87%) were emergent and performed outside regular hours. Anesthesiologists were required to deal promptly with these patients. When dealing with patients with severe hepatic encephalopathy, continuous hemodiafiltration is also needed during LDLT, thus requiring the participation of an anesthesiologist in their management.

Outline of liver transplantation procedure

For the anesthetic management of LDLT, it is essential that the anesthesiologist is well informed in advance about the outline of the planned surgery. The following is an outline of recipient surgery as it is conducted at Kyoto University Hospital. After celiotomy, the hepatic artery, the portal vein, and then the hepatic veins are dissected, followed by removal of the diseased liver. The liver graft is inserted, followed by anastomosis, first to the hepatic vein and then to the portal vein, after which portal blood flow is resumed. Next, the hepatic artery is reconstructed by microscopic surgery (a loupe has sometimes been used in recent years when the patient is an adult), followed by reconstruction of the biliary tract, for which anastomosis of the donor common bile duct to the jejunum limb of a Roux-en-Y anastomosis is the technique of choice. In cases of right-lobe transplantation, where the patient's own bile duct can be used, end-to-end anastomosis of donor and recipient common duct is sometimes selected.

Recipient surgery can be divided into three phases: (1) the preanhepatic phase (from skin incision to dissection of the portal vein), (2) the anhepatic phase (until resumption of portal blood flow through the liver graft), and (3) the postanhepatic phase (from resumption of portal blood flow to the end of surgery). In patients with biliary atresia who have undergone a number of operations, or in patients receiving re-transplantation, intraperitoneal adhesion is often intense and collateral circulation development is marked. This often requires much time for manipulation during the preanhepatic

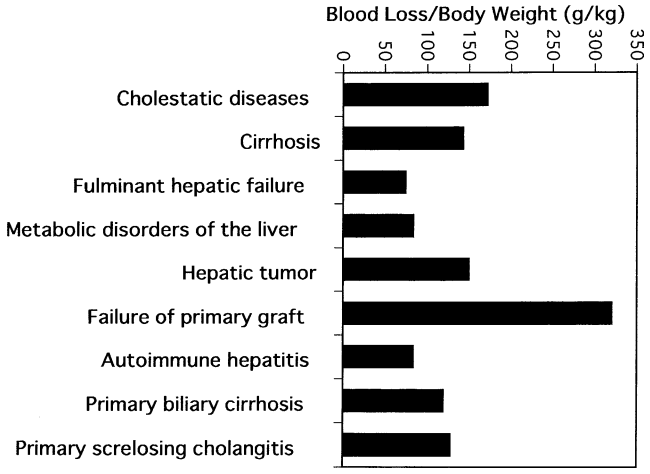

Fig. 2. Mean intraoperative blood loss for patients, grouped by underlying disease, who had undergone LDLT at Kyoto University Hospital by the end of October 2001

phase, or it causes massive bleeding. In previously unoperated patients without intraperitoneal adhesion or in those with fulminant hepatic failure, metabolic disease, or other conditions where collateral development is poor, manipulation during the preanhepatic phase usually does not take much time, and massive bleeding is unlikely to occur. Figure 2 shows the volume of blood lost per body weight by disease group.

Unlike transplantation of the entire liver from a brain-dead donor, in which replacement of both the inferior vena cava and the liver is often performed at the same time, for LDLT, there is a need to free the liver from the inferior vena cava. This manipulation sometimes causes massive bleeding or air embolus. According to studies published in Western countries, an air embolus during brain-dead donor total liver transplantation often develops when the liver graft is reperfused [3]. However, of the 12 cases of air embolus we encountered, all but 2 developed during dissection of the liver from the inferior vena cava.

Resumption of the portal blood flow sometimes induces hypotension, known as "post-reperfusion syndrome". This will be discussed later in this article. During LDLT, the liver graft has high viability, and the coagulation gradually improves in the postanhepatic phase, so that anesthetic management is usually smooth. However, in patients in whom intestinal adhesion is severe, much time is needed to free the adhesion in this phase.

The procedures used for LDLT at Kyoto University Hospital can be roughly divided, by the type of graft, into left-lobe transplantation (548 cases) and right lobe transplantation (209 cases). When domino transplantation was performed, 2 patients underwent transplantation of the entire liver. One patient underwent dual-liver transplantation (right lobe and lateral segment) from two donors. In terms of anesthetic management of the recipient, there is little difference between left-lobe and right-lobe LDLT.

Auxiliary partial orthotopic liver transplantation (APOLT) is a special technique for LDLT. It has been used in 29 cases at our hospital—to preserve the right lobe and graft the left lobe in 27 cases, and to preserve the left lobe and graft the right lobe in 2 cases. This procedure was first used in Europe for the treatment of fulminant hepatic failure and is aimed at overcoming the acute crisis by means of liver transplantation and subsequently allowing the patient's own liver to regenerate. At Kyoto University Hospital, the primary purpose of APOLT has been to make up for insufficient liver graft capacity. In some cases where APOLT was used, the patient's own liver was removed after the volume of the liver graft had increased [4]. However, because APOLT requires complex manipulation, blood loss tends to be greater and the operation time to be longer. Since right-lobe LDLT began to be used in 1998, the number of patients treated with APOLT has been decreasing at our hospital.

Anesthetics and muscle relaxants

LDLT is usually performed as an elective surgery, so that the patient can be fasted for a sufficient length of time before surgery. We usually do not give premedication for patients receiving LDLT. Anesthesia is induced by intravenous administration of an anesthetic (propofol) and a muscle relaxant via the route secured on the previous day for the intravenous administration of fluid. This applies also to children. If the patient has a history of gastrointestinal bleeding due to esophageal varices, compression of the cricoid cartilage is performed. For anesthesia we selected a combination of isoflurane and fentanyl (60 cases; 8%), of midazolam and fentanyl (223 cases; 29%), or of propofol and fentanyl (477 cases; 63%). All these combinations have been reported to have few side effects on liver function. When total intravenous anesthesia is used, the blood levels of the anesthetics are theoretically expected to rise during the anhepatic phase. However, when the anhepatic phase lasted for only about 2 h, the blood propofol level did not rise significantly during this phase, even when the dose level was kept constant. When the anhepatic phase was longer (over 5 h), however, some patients showed a gradual rise in the blood propofol level. The rise in the blood propofol level was clearly reflected in the fall in the bispectral index (BIS) in these patients. Therefore, the dose level of anesthetics can be regulated by using the BIS as an indicator. Nitrous oxide was not used, on the grounds that it can

increase the gas volume within the intestine, thus possibly leading to compression of the hepatic blood vessels and exacerbation of air embolus.

Alcuronium (37 cases; 5%), pancuronium (118 cases; 16%), or vecuronium (605 cases; 80%) were used as muscle relaxants. Because vecuronium is eliminated by and degraded in the liver, the duration of its action is affected by liver function. Therefore, if a muscle relaxant monitor is used, the dose of this drug needed to maintain a certain level of muscle relaxation during the anhepatic phase can be reduced [5]. Because we did not always use a muscle relaxation monitor during surgery, it is possible that unnecessarily high doses of muscle relaxants were administered during the anhepatic phase. However, there were no cases where residual effects of the muscle relaxants caused a problem during postoperative management in the ICU.

Monitoring and intraoperative tests

As for other major surgical operations, we continuously monitored ECG, invasive arterial pressure, central venous pressure (CVP), pulseoximetric saturation, carbon dioxide tension in expired gas, urinary volume, and core temperature during LDLT. As a rule, catheterization of the pulmonary artery was performed for patients weighing over 40 kg who were expected to develop massive bleeding in view of their disease type, history, etc., and for patients with severe pulmonary shunt (194 cases in total). In recent years, however, we have attached primary importance to the prevention of infection, and catheterization of the pulmonary artery has not been performed, except in some special cases, such as in patients with pulmonary hypertension. Although the prevalence of cardiac dysfunction is low among patients undergoing LDLT, monitoring invasive arterial pressure and CVP is essential, because LDLT involves major blood loss. Measuring the carbon dioxide tension in expired gas is useful when checking for air embolus. Because the liver graft has been cooled when it is inserted into the peritoneal cavity, body temperature is likely to decrease during LDLT. Considering that the core temperature would be inaccurate if the thermistor was directly affected by the intraperitoneal temperature, either the esophageal temperature is measured (with a thermistor with the tip located within the thoracic cavity) or the blood temperature is measured via a pulmonary artery catheter.

For adult patients, the portal venous pressure is sometimes monitored with a catheter inserted via the operative field. The normal range of the portal venous pressure is under 20 mmHg. In patients in whom the portal venous pressure rises abnormally during the postanhepatic phase, we need to consider the possibility of outflow block of the hepatic vein or other complications, and may request the surgeon to check the blood flow through the liver graft by means of Doppler ultrasonography.

To determine the volume of blood to be transfused; to correct for acidosis, abnormal electrolytes, abnormal blood glucose level, and hypoalbuminemia associated with liver dysfunction; and to regulate coagulation, we usually perform hematological tests every hour. These tests include blood cell counts, blood gas analysis, and measurement of serum electrolytes, blood glucose, serum lactic acid, prothrombin time (PT), partial thromboplastin time (APTT), and activated coagulation time (ACT). Measurements with a celite-activated viscometer (Sonoclot; Sienco, Wheat Ridge, CO, USA) are performed every 2 h to assess not only the coagulation but also the platelet function and the fibrinolytic system. Total protein; albumin; liver enzymes, such as GOT (AST) and GPT (ALT); and indicators of renal function, such as blood urea nitrogen (BUN) and creatinine, are generally also measured every 2 h. The blood levels of liver enzymes rise after reperfusion of the liver graft, but they usually remain below 1000 IU/l. In cases where a fatty liver has been donated or where brain-dead donor partial liver transplantation is performed by dividing the live graft on the back table, blood levels of liver enzymes rose to over 1000 IU/l during surgery, probably reflecting ischemic damage to the liver graft.

Prevention of infection

The first requirement for anesthesiologists to prevent infection during LDLT is to take the usual, standard precautions. When inserting a catheter into the central vein, anesthesiologists must scrub their hands, wear a sterile gown and sterile gloves, and use a clean 120 × 120-cm cloth with a hole to cover the patient's body. When inserting an arterial line, we also make it a rule to disinfect the skin with povidone iodine and to use sterile gloves and a sterile cover cloth. Immediately before prophylactic antibiotics are administered prior to surgery, histamine H1 and H2 receptor antagonists are intravenously administered to reduce symptoms of anaphylaxis, which can be caused by antibiotics, and to prevent intraoperative stress ulceration. To simplify the cleaning procedure for the venous and arterial lines, closed circuits are usually employed for IV infusion and arterial lines.

Immunosuppressors and other drugs

Methylprednisolone (10 mg/kg) is the only immunosuppressor that is administered by anesthesiologists

during this surgery at our hospital. This drug is administered, together with urinastatin (urinary trypsin inhibitor), during portal anastomosis after completion of the anastomosis of the hepatic vein. For children, oral administration of tacrolimus as an immunosuppressor is initiated on the day before surgery, but it is not used during surgery. Prostaglandin E1 (PGE1) preparation is not administered routinely for liver protection, but only when a fatty liver is used as a graft or when there is ABO incompatibility between the donor and the recipient blood type. In recent years, continuous infusion of a PGE1 preparation ($0.01\,\mu g \cdot kg^{-1} \cdot min^{-1}$) and gabexate mesilate ($40\,mg \cdot h^{-1}$) is initiated during anastomosis of the hepatic artery and administered via a portal vein catheter for ABO incompatible adult patients.

IV fluid and blood transfusion

Acetated Ringer's solution is used as the basic IV solution. One of the drip infusion routes is supplemented with glucose to avoid hypoglycemia. Because acetic acid is degraded in skeletal muscles as well as in the liver, it is suitable as a pH buffer for patients with hepatic failure. An adequate glucose supply is indispensable during the preanhepatic and anhepatic phases, because hypoglycemia is likely to develop due to disturbed gluconeogenesis during these phases. During the postanhepatic phase, however, glucose administration can cause hyperglycemia. Because of loss into ascites, plasma protein fraction (PPF) or 25% human albumin needs to be administered to maintain plasma albumin and colloidal osmotic pressure at normal levels. As a rule, we administer PPF or 25% albumin at a dose that will keep the albumin level at about $3\,g \cdot dl^{-1}$. The dose of PPF during LDLT is generally higher than that for other surgical procedures. The mean volume of IV fluid used is $15.8\,ml \cdot kg^{-1} \cdot h^{-1}$, and an average of $10.4\,ml \cdot kg^{-1} \cdot h^{-1}$ of this volume is accounted for by colloid.

For blood transfusion, we make it a rule to transfuse RC-MAP blood, with the aim of keeping hematocrit at about 30%; FFP is administered if PT exceeds 20 s. The data collected at Kyoto University indicate that the amount of FFP administered shows a significant correlation with the postoperative onset of hepatic artery thrombosis [6]. For this reason, we avoid unnecessary administration of FFP, so that the percentage of patients who received no FFP during LDLT was 66% (314/479) for children younger than 15 years and 38% (107/281) for patients 15 years of age or over.

LDLT involves major blood loss. At Kyoto University, an average of 155 g blood is lost per kg body weight, equivalent to 2.2 times the circulating blood volume. However, as mentioned earlier, the volume of blood loss varies greatly, depending on the type of underlying disease, disease history, etc. There were 33 patients who received no transfusion of blood (including FFP) during LDLT, and 1 patient who received transfusion of his own blood pooled in advance. As a rule, we are ready to transfuse RC-MAP in a volume of one $unit \cdot kg^{-1}$, and this volume is increased in patients in whom massive bleeding is likely to occur (e.g., patients receiving retransplantation). To prevent the onset of graft-versus-host disease (GVHD) after surgery, gamma-ray irradiation (25 Gy) is administered to every blood product. Furthermore, to prevent infection or re-infection with cytomegalovirus, blood is transfused through a leukocyte filter. A vein in the upper half of the trunk is used as a route for IV fluid and blood transfusion, because the inferior vena cava can be injured or occluded during liver transplantation. A cubital or forearm vein, which is as large as possible, is used as a peripheral route for IV fluid and blood transfusion for all child patients (usually 20 G), and two such veins are selected for each adult (usually 14–16 G). In patients in whom extremely marked blood loss is expected, one or two additional peripheral routes are secured. For children, the central vein is secured with a 5-Fr triple-lumen catheter (5 or 8 cm) inserted via the right internal carotid vein. The diameter of the maximum lumen of this catheter is 18 G. When needed, this route is utilized for the rapid transfusion of PPF.

For children with low body weight, the absolute volume of blood loss is not very large even when massive bleeding occurs, so that can be satisfactorily dealt with by pumping with a syringe. However, if massive bleeding occurs in adults, the absolute volume of blood loss is large, often making it difficult to cope with. The largest volume of blood loss we have encountered to date was 84240 g in a 14-year-old female with a body weight of 42.6 kg. In this patient, pumping with a syringe combined with a leukocyte filter was inadequate, and the leukocyte filter had to be removed from the route. Furthermore, the supply of RC-MAP preparations could not meet the demand. For this reason, recycling autologous blood transfusion was initiated during surgery, even though an infectious embolus had developed in the portal vein [7]. As a result of the massive bleeding and transfusion, the body temperature of this patient dropped to 31.4°C during surgery. Fortunately, however, this patient survived and was eventually discharged. After this experience, we adopted a new blood transfusion/IV fluid warming system to heat the fluid in a 42°C circulating water bath before it enters the patient's body, and allow for rapid transfusion via a leukocyte filter. In a recent patient in whom 70550 g of blood was lost, the use of this system resulted in suppression of the decrease in body temperature, keeping it above 35.0°C, and in successful management without removal of the leukocyte filter [8].

Cardiovascular management

Patients with terminal-stage liver cirrhosis are often in a hyperdynamic state characterized by high cardiac output and low peripheral vascular resistance. In children, it is rare that catecholamines need to be used during surgery, and the administration of dopamine at a dose of up to about $5\,\mu g \cdot kg^{-1} \cdot min^{-1}$ usually suffices. In adults with terminal-stage liver cirrhosis, it is sometimes difficult to maintain blood pressure unless norepinephrine or epinephrine is administered on the basis of data collected with the pulmonary artery catheter. Even in these patients, circulation tends to gradually stabilize after portal reperfusion, and norepinephrine or epinephrine can usually be discontinued by the end of surgery.

Citric acid contained in blood preparations is degraded in the liver. For this reason, patients with compromised hepatic function who are going to receive liver transplantation often show abnormally low ionized calcium levels in blood due to elevated blood citric acid levels. RC-MAP blood, which has recently been used as an erythrocyte preparation, contains less citric acid than conventional citrate-phosphate-dextrose (CPD) blood. Nevertheless, the citric acid it does contain can cause problems when there is a massive blood transfusion. FFP contains an amount of citric acid equal to that contained in conventional preparations. Therefore, when performing liver transplantation, measurement of ionized calcium level has proven indispensable for the prevention of reduced cardiac function due to low blood ionized calcium levels, which are corrected by administering calcium chloride.

Transplantation of the entire liver from a brain-dead donor involves transplantation of the inferior vena cava together with the liver and thus needs clamping of both the inferior vena cava and portal vein. To prevent a reduction in venous return, a veno-venous bypass is usually employed. When LDLT is performed, the hepatic vein is dissected, usually without complete obstruction of the inferior vena cava. In recent years, a technique that does not involve complete clamping of the inferior vena cava (the piggyback method) has been used with increasing frequency, even for transplantation of the entire liver from a brain-dead donor. This technique was also used for our patients.

Patients with terminal-stage liver cirrhosis show marked collateral circulation development. For this reason, hemodynamics vary little in the anhepatic phase following obstruction of the portal vein. However, in patients with metabolic disease or fulminant hepatic failure, no collaterals are developed, so that the portal venous obstruction has a major effect. The anhepatic phase should, therefore, be as short as possible. When it is difficult to shorten the anhepatic phase, due to the timing of surgery in the donor, a portal vein-inferior vena caval shunt is created. In this way, a reduction in circulating blood volume and congestion of the intestine due to portal venous obstruction can be prevented.

Anastomosis of the hepatic vein involves side-clamping of the inferior vena cava. After anastomosis of the hepatic vein is finished, a clamp is applied again to the hepatic vein, and the clamp to the inferior vena cava is released, so that the inferior vena cava is not clamped for very long. In some patients (especially in children), however, even side-clamping can cause almost complete obstruction of the inferior vena cava. In such patients, IV fluid, blood, or catecholamine needs to be administered to maintain blood pressure, but when doing so, care needs to be taken that these preparations are not administered in extremely excessive volumes, because the circulating blood volume may become abnormally high after portal reperfusion. This means that careful cardiovascular management, including monitoring of the CVP, is essential.

Reperfusion of the liver graft can lead to sharp changes in hemodynamics, such as hypotension and bradycardia. This condition is known as post-reperfusion syndrome, but its cause is not known. The percentage of patients in whom the mean arterial pressure falls to below 70% within 5 min of reperfusion is reported to be 8%–30% [9]. Of our patients who underwent liver transplantation, 125 patients (16.4%) showed a decrease in blood pressure to below 70% of the baseline level after reperfusion. In spite of correction of circulating blood volume, electrolytes, acid-base balance, etc., before reperfusion, hypotension following reperfusion could not always be avoided, although no serious problems such as cardiac arrest occurred. Blood pressure that fell once after reperfusion usually returned to the baseline level within a few minutes, unless bleeding from the anastomosed site occurred.

Respiratory management

It is reported that patients with terminal-stage hepatic failure who receive liver transplantation often have respiratory complications during the perioperative period. Major complications observed at our hospital have been atelectasis, pneumonia, and pleural effusion, both before and after surgery. In patients in whom ascending cholangitis is identified as a cause of fever, LDLT is performed as scheduled. Accordingly, complications caused by mild inflammation of the upper airway are not uncommon, and atelectasis following induction of anesthesia was detected on chest X-rays in about 6% of children and required treatment with a bronchofiberscope or other means. During surgery, the oxygen concentration in inspired gas is kept between 30%–40%

and *P*aO2 is maintained above 100 mmHg by means of intermittent positive-pressure ventilation. In view of the need for continuous mechanical ventilation for many hours, standard positive end-expiratory pressure (PEEP; 2 cmH_2O) is performed to avoid microatelectasis. Because hypocapnia can reduce hepatic blood flow, the ventilation is set at a level where $PaCO_2$ can be kept within the normal range (35–45 mmHg). To keep the airway moist during surgery, an artificial nose equipped with a bacterial filter is used for both children and adults.

As mentioned earlier, there were 17 patients with preoperative complications caused by pulmonary shunts. In such patients, the oxygen concentration of the inhaled air is permitted to reach a maximum of 100%, and the PEEP level is increased to a maximum of 5 cmH_2O to keep arterial oxygen tension above 100 mmHg during surgery. Because the pulmonary shunt rate becomes exacerbated after reperfusion, PGE1 preparations, which can exacerbate shunt, are not used. After surgery, the patient is weaned from mechanical ventilation when it appears that the preoperative oxygen saturation level in room air can be maintained with oxygen inhalation only. Several months or more are usually needed before the pulmonary shunt can be improved [10].

Hypoxemia during surgery is caused by, among other factors, asthmatic attacks and difficulties with the tracheal tube. In addition to these causes of hypoxemia experienced during ordinary surgery, air embolus may result in hypoxemia during liver transplantation. So far, we have encountered 12 cases of intraoperative air embolus. In one patient, it was caused by air flow from the anastomosed site of the hepatic vein after portal reperfusion. The diagnosis of air embolus can be easily confirmed by checking for a sharp reduction in expired gas carbon dioxide tension and by checking for any surgical manipulations which may have induced air embolus. If air embolus does occur, the inferior vena cava should be immediately clamped at a point above the air entry point. This is followed by elevating the oxygen concentration of the inhaled air to 100%, elevating the PEEP level, and attempting to aspirate the air through the central venous line or the pulmonary artery catheter with the patient's head raised. One child developed two episodes of marked ST elevation on ECG following paradoxical air embolus, probably through a patent foramen ovale, which seems to have led to myocardial ischemia due to air embolus of the coronary artery [11]. Fortunately, this patient could be discharged without sequelae, but fatal cases of paradoxical air embolus have been reported in the literature [12]. When dealing with such cases, increasing the PEEP level should be avoided, because it can precipitate the transfer of air into the systemic circulation.

Coagulation management

Coagulation factors are mostly produced in the liver, so that patients with hepatic failure often show disorders of coagulation. During surgery, coagulation may be further reduced during the anhepatic phase and by loss of coagulation factors caused by bleeding. When necessary, coagulation factors are replenished by the administration of FFP according to the rules outlined above. For children with metabolic and other diseases, whose coagulation is normal and who do not show prolonged PT during the anhepatic phase, we administer heparin to prevent hepatic artery thrombosis. Because the effects of heparin are unlikely to be reflected in the PT, we use ACT (more than 150 s) and APTT (more than 180 s) as indicators. During surgery, antithrombin III (ATIII) level and activity are monitored, and concentrated ATIII is administered if they are abnormally low.

It is thought that a hemorrhagic tendency is precipitated by enhanced fibrinolysis following reperfusion of the liver graft. It has been reported that the administration of aprotinin (a drug which exerts antifibrinolytic action by inhibiting plasmin) reduced blood loss during brain-dead donor liver transplantation [13]. As already described in the section on Monitoring, Sonoclot is used to evaluate the fibrinolytic function, but even when signs suggestive of enhanced fibrinolysis are observed, antifibrinolytic agents are not always routinely administered at our hospital. We use tranexamic acid only when surgical control in the operative field seems difficult, in addition to enhanced fibrinolysis monitored by Sonoclot.

Body temperature control

During liver transplantation, hypothermia can occur frequently, due to factors such as the wide operative field, massive bleeding, and long operation time. Children are more likely to develop hypothermia, because their body surface area per body weight is greater than that of adults. In addition, hypothermia can exacerbate coagulation disorders and cardiac dysfunction. For this reason, several measures are taken to maintain body temperature, such as adjustment of the room temperature, heating the IV fluid and blood before transfusion, using a heated mattress, and wrapping the extremities. The circuit for the rapid infusion of IV fluid is combined with a heating device which heats the fluid in a 42°C rotating water bath until the fluid enters the patient's body, the same procedure as that used for the rapid blood transfusion circuit. The body temperature decreases even further when the liver graft, which has been stored at low temperature, is reperfused. However, this decrease in body temperature is small, and

suppression of circulation and other adverse effects can be prevented if the body temperature is kept normal until reperfusion takes place. In children, body temperature often rises excessively during biliary tract reconstruction, thus making cooling necessary.

Electrolyte control

In patients with liver cirrhosis, electrolyte abnormalities are often seen as a result of the preoperative use of diuretics and the hyperaldosteronemia associated with cirrhosis. In brain-dead donor liver transplantation, blood potassium levels rise rapidly following reperfusion of the liver graft. For this reason, it has been recommended to avoid correction of mild hypokalemia during surgery [9]. Examination of the patients scheduled to receive LDLT at our hospital has indicated that about half have low blood sodium, potassium, and magnesium levels before surgery. Examinations 10 min before and after reperfusion of the liver graft have shown that changes in electrolyte levels are minimal. We recently encountered a patient in whom Torsades de Pointes developed during the anhepatic phase, and hypomagnesemia seemed to be one of the factors responsible for this. We therefore make it a rule to take measures for correcting electrolyte abnormalities before reperfusion of the graft for liver transplantation patients.

Procedures from the end of surgery to weaning off mechanical ventilation

It is not impossible to have patients recover consciousness and wean them off mechanical ventilation in the operating room soon after the operation of liver transplantation is completed. In fact, some facilities in Western countries routinely wean patients off mechanical ventilation in the operation room. At our hospital, however, we make it a rule to do so the next morning or later, and to continue mechanical ventilation during the night following the day of the operation, for reasons of safety, because surgery often ends late at night at our hospital. Weaning from mechanical ventilation following liver transplantation is not more difficult than that after ordinary surgery involving celiotomy, except for patients with preoperative hepatic encephalopathy, poor postoperative functioning of the liver graft, massive intraoperative bleeding, or hepatopulmonary syndrome. Propofol is generally used for patients who need to remain sedated until the next morning.

Donor surgery

Needless to say, it is essential to secure the safety of the donor for LDLT. While LDLT donor deaths have been reported in the United States and Germany, no such death has been reported in Japan. By the end of 2001, we had anesthetized 755 donors, excluding donors for domino transplantation, and encountered only one case of air embolus as a severe intraoperative complication and one case of postoperative pulmonary embolus [14], but no cases of severe sequelae after donor surgery.

Depending on the type of graft, donor surgeries performed at our institution can be divided into lateral segmentectomy (380 cases), extended lateral segmentectomy (41 cases), left lobectomy (124 cases), and right lobectomy (209 cases). The average blood loss during donor surgery was 321 g (range, 10–2300 g) and did not show marked differences among operative procedures. To avoid homologous blood transfusion, we started reserving the donor's own blood (800–1200 ml) prior to donation surgery, and, as our experience with this surgery increased, the volume of blood reserved could be reduced to 400 ml. Starting with the 373rd case, however, we stopped reserving the donor's own blood before lateral segmentectomy for the following reasons: (1) a blood reserve of this volume (400 ml) is not really useful; (2) in most cases the volume of blood lost was smaller than the volume reserved; (3) collecting blood to be reserved is burdensome for the donor, who is usually hospitalized on the day before surgery; and (4) the number of donors who must undergo urgent donation surgery, which does not allow for preoperative blood collection, has been increasing. In 1998, the first right lobectomy was performed. Since then, acute normovolemic hemodilution has been performed for donors undergoing urgent surgery or those in whom no blood had been reserved for right lobectomy. However, because the average volume of blood lost during right lobectomy was less than 400 g, we discontinued reserving blood and performing acute normovolemic hemodilution for all individuals undergoing donor surgery after 1999. For all individuals undergoing donor surgery, however, preoperative type and screen procedures are performed.

Donor surgery is usually performed with general anesthesia combined with epidural anesthesia. It is similar to that used for ordinary hepatectomy, except for the intravenous administration of heparin (1000 units), which is performed immediately before graft perfusion to prevent thrombosis of the liver graft. For all cases, an invasive arterial line is secured, in addition to a peripheral route for IV fluid, but, as a rule, no central venous line is inserted.

Conclusion

Although the number of patients receiving liver transplantation has been increasing, this surgery still involves a high risk of massive bleeding and severe intraoperative complications. The anesthesiologist in charge of liver transplantation needs to make adequate preparations, while bearing in mind the preoperative condition of each patient, the planned operative procedure, and other features associated with this type of surgery.

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