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REVIEW ARTICLE

ANESTHETIC MANAGEMENT OF PATIENTS UNDERGOING LIVING DONOR LIVER TRANSPLANTATION

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ABSTRACT

Living donor liver transplantation (LDLT) is now routinely performed upon a lack of liver grafts from deceased donors. In addition to surgical technique, anesthetic management for LDLT is also important for both the safety of recipients and good surgical outcomes. Three phases, which are preanhepatic, anhepatic, and neohepatic phases, constitute the process of LDLT. Recipients, who already have physiological derangements caused by a nadir of hepatic function, encounter physiologically challenging conditions specific to each phase. Therefore, induction and maintenance of anesthesia and hemodynamic monitoring during the anesthesia should be tailored to patients' underlying medical conditions and physiological challenges associated with surgical procedures performed during each phase. In this regard, this review will deal with anesthetic managementof recipients undergoing LDLT, particularly according to each phase.

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INTRODUCTION

Since living donor liver transplantation (LDLT) was successfully performed in a pediatric recipient in 1989 (Strong *et al*., 1990) following the first LDLT in which the recipient did not survive (Raia *et al*., 1989), it has optimized timing of transplantation by minimizing graft preservation time and added a healthy live donor graft, which has never been subjected to the adverse physiologic conditions, to the deceased donor graft pool. In this review, the anesthetic management of LDLT recipients (especially according to the phases of the surgery) will be discussed.

Induction of anesthesia

Sedative premedication should be avoided especially in the patients with hepatic encephalopathy, who are very sensitive to the effects of sedative medications (particularly benzodiazepines). Standard monitoring which includes pulse oximetry, noninvasive blood pressure, and electrocardiogram monitoring is instituted before the induction of anesthesia. Additionally, electroencephalogram-based monitoring (e.g., bispectral index, patients state index, state and response entropy) and radial artery catheter, which allow easier titration of depth of anesthesia and real-time blood pressure monitoring respectively, can be placed when unstable hemodynamic response to induction agents are anticipated.The choice of intravenous induction agents such as propofol, thiopental, or etomidate with or without opioids (e.g., remifentanil, fentanyl, alfentanil, sufentanil, etc.), and neuromuscular blocking agents facilitating endotracheal intubation usually depends on the preference of the attending anesthesiologists. Rapid sequence induction is often warranted because of delayed gastric emptying or increased intra-abdominal pressure from ascites.

Intravascular catheterization for hemodynamic monitoring and administration of fluid and medications

In addition to radial artery catheterization performed most commonly for arterial blood pressure monitoring and repeated arterial blood sampling because of its superficial location offering easy accessibility for catheterization and the low incidence of complications (Frezza and Mezghebe, 1998), femoral artery catheterization is also mandatorybecause relatively well maintained femoral (central) systolic blood pressure compared to radial artery systolic blood pressure during the reperfusion phase prevents unnecessary administration of vasoconstrictors, which occurs when only

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radial systolic blood pressure was monitored during the reperfusion phase (Arnal *et al*., 2005). Femoral venous pressure is useful to monitor the venous return from inferior vena cava (IVC) to right atrium. Increased femoral venous pressure with unchanged or slightly decreased central venous pressure (CVP) measured from internal jugular vein catheter is observed when the venous return from the IVC to the right atrium is impaired due to 1) manipulation of the native liver to mobilize it and identify its vascular structures during the dissection phase and 2) partial clamping of the IVC during the anhepatic phase. Intravenous catheters to transfuse large volumes of colloid and blood products are placed in the right internal jugular or subclavian veins. The Swan-Ganz Continuous Cardiac Output (CCO) thermodilution flow-directed pulmonary artery catheters (Edwards Lifesciences, Irvine, USA) allow for continuous cardiac output and mixed venous oxygen saturation monitoring, when used with the Vigilance monitors (Edwards Lifesciences, Irvine, USA). Alternatively, an intra-arterial catheter connected to the Flotrac^{TM} sensor (Edwards Lifesciences, Irvine, USA) and PreSep Central Venous Oximetry Catheter (Edwards Lifesciences, Irvine, USA) provide real-time information on cardiac output, central venous oxygen saturation, and dynamic preload index (stroke volume variation), when used with the EV1000^{TM} monitor (Edwards Lifesciences, Irvine, USA).

Dissection (preanhepatic, paleohepatic) phase

The dissection phase begins with surgical incision and ends with cross-clamping of the portal and hepatic veins and hepatic artery. As hypotension often develops following acute decompression of ascites, adequate fluid replacement using colloid such as albumin is crucial to maintain the hemodynamic stability and plasma oncotic pressure with albumin level at more than 3 g/dl. Similarly, manipulation of the liver to identify the vascular and biliary structures and dissect adhesions between the liver, diaphragm, and retroperitoneal areas can impede venous return to the right atrium resulting in hypotension. A lower CVP facilitates hepatic venous drainage from the liver and may reduce bleeding during the dissection phase. However, the possibility of an air embolism resulting from injury to the IVC or hepatic veins and accompanying renal compromise must be weighed against the benefit derived from lowering CVP. Thus, there exists controversy regarding an optimal CVP value for recipients. Lowering CVP by approximately 40% of the baseline value did not increase the number of renal complications or the length of hospital stay, improved 1-year survival rate (Massicotte *et al*., 2006), facilitated blood salvage with decreased secondary transfusion, and protected liver function (Feng *et al*., 2010). In contrast, there were elevated levels of creatinine, a more frequent need for dialysis, and increased mortality when CVP was maintained at < 5 mmHg (Schroeder *et al*., 2004).

Anhepatic phase

The anhepatic phase begins with excision of the native liver and ends with reperfusion of the graft. The piggyback technique, which preserves flow through the partially patent IVC and consequently achieves hemodynamic stability, is currently the most widely used technique in the world for liver transplant surgery. When aggressive fluid administration is implemented to maintain adequate blood pressure during the anhepatic phase, the return of congested portal blood flow from the intestines following the release of vascular clamps may result in fluid overload which impairs hepatic venous outflow and portal venous inflow and consequently leads to the engorgement of the hepatic allograft and intestines. The swollen liver and intestines may cause a significant technical challenge of Roux-en-Y choledochojejunostomy. A failure to clear citrate and lactate, which normally is metabolized by the liver, results in hypocalcemia and lactic acidosis (Merritt, 2000). Calcium infusion using calcium chloride or calcium gluconate is frequently required (Martin *et al*., 1990) because citrate-associated hypocalcemia is aggravated following massive transfusion of blood products in the absence of the native liver. If the use of sodium bicarbonate is considered to manage lactic acidosis, it should be administered cautiously because high sodium loads, which may cause rapid swings in serum sodium, or even hypernatremia, pose hyponatremic cirrhotic patients at risk for central pontine myelinolysis which is a neurologic condition characterized by symmetric noninflammatory demyelinating lesions resulting from osmotic stress on central nervous system cells in the basis pontis. The recommended rate of sodium correction is 12 mEq/L/day.

Reperfusion (postanhepatic, neohepatic) phase

Hemodynamic instability and even cardiac arrest, which refer to postreperfusion syndrome manifesting with reduced cardiac contractility (Webster *et al*., 1994), arrhythmias, severe bradycardia, and profound hypotension, can occur within seconds to minutes of unclamping of the portal and hepatic veins. The anesthetic management is directed at maintaining or recovering hemodynamic stability using inotropes, chronotropes, and vasopressors. Although the underlying mechanism is unknown and remains elusive, high potassium loads from the preservative solution (University of Wisconsin solution) (Muhlbacher *et al*., 1999), increased age of the liver graft donor (Ramsay, 2008), decreased systemic vascular resistance, hypothermia, metabolic acidosis, endogenous vasoactive peptides such as interleukin 6, tumor necrosis factor α, potassium and hydrogen ions, and emboli (Paugam-Burtz *et al*., 2009), and sudden atrial stretching in response to unclamping and reperfusion are postulated to produce the hemodynamic instability. The acid-base imbalance improves and the calcium requirement is reduced with graft metabolism of citrate and lactate within 30 minutes after the reperfusion. The cardiac output decreased following an acute increase after the reperfusion and systemic vascular resistance increase as the allograft metabolizes vasoactive substances within the first hour. Bile is produced in 30 minutes after the reperfusion. Because renal vasoconstrictors are metabolized by the graft, renal function improves. Impaired insulin-mediated glucose uptake in patients with chronic end-stage liver disease usually causes hyperglycemia that is worsened in the reperfusion phase by enhanced glycogenolysis by the graft liver, decreased glucose use, and insulin resistance (Merritt, 2000; Shangraw and Hexem, 1996). Prostaglandin E_1 is continuously infused in expectation of hepatic cytoprotection (Peltekian *et al*., 1996) and reduction in the risk of death, primary non-function of the allograft, re-transplantation, or acute kidney injury (Cavalcanti *et al*., 2011). Despite the possibility of inadequate intraoperative tissue perfusion to various organs, particularly to the kidneys, lowering CVP was recommended in LDLT because maintenance of high CVP during the reperfusion phase may impair hepatic venous outflow, potentially jeopardizing graft function. However, the value of this filling pressure has been questioned and stroke volume variation, one of the dynamic preload indices, has been advocated for fluid management in mechanically ventilated patients undergoing

LDLT (Biais *et al*., 2008; Kim *et al*., 2013). Nevertheless, recently, CVP was found to be negatively correlated with peak portal vein flow velocity which was measured using spectral Doppler ultrasonography immediately after hepatic artery anastomosis and bile duct reconstruction in the patients without vascular complications (Kim *et al*., 2013).

Clinical immunosuppression

Immunosuppressive drugs are divided into two groups: agents used for induction therapy immediately after transplantation and those used for maintenance therapy. As an induction therapy agent, basiliximab, which is a chimeric anti-CD25 monoclonal antibody, inactivates T-lymphocytes by binding to the α chain of their interleukin 2 receptor and consequently prevents allograft rejection. 1) Tacrolimus (formerly known as FK-506), which blocks the phosphatase activity of calcineurin involved in regulation of interleukin 2 gene expression, and 2) mycophenolate mofetil, which inhibits inosine monophosphate dehydrogenase and blocks the proliferation of lymphocytes, are used for maintenance of immunosuppression. Due to unaccepted side effects resulting from prolonged use, such as hypertension, weight gain, peptic ulcers and gastrointestinal bleeding, euphoric personality change, cataract formation, hyperglycemia that could progress to diabetes, pancreatitis, muscle wasting, and osteoporosis with avascular necrosis of the femoral head, current protocols use adrenal corticosteroids for less than 7 days despite their potent immunosuppressive actions.

Conclusion

Comprehensive understanding of surgical procedures performed during each phase and anesthetic management of the accompanying physiologic and metabolic perturbations is essential to yield clinically beneficial results in the patients undergoing LDLT.

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