Liver transplantation: an adventure for the anaesthesiologist

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Abstract

Introduction
Liver transplantation has become the treatment of choice for end-stage liver disease and some cases of acute liver failure. The procedure is extremely complex and requires excellent surgical technique and experienced anaesthesiologists. Patients undergoing liver transplantation have severe liver disease characterized by multisystem disorders that pose many anaesthetic challenges. Due to this fact, extensive preoperative assessment is required. A detailed monitoring of the patient and a careful therapeutic concept is necessary to meet the extraordinary challenges posed by this exciting adventure called liver transplantation. The aim of this review was to discuss the role of the anaesthesiologist in liver transplantation.

Conclusion
Liver transplantation has evolved over the years. Survival is still increasing gradually in relation to greater expertise in the surgical procedure and management of immunosuppressive therapy. Still, further studies are needed in areas of haemodynamic monitoring, blood and coagulation management to prove its efficiency.

Introduction

“Life is either a daring adventure or nothing.” — Helen Keller

Liver transplantation (LTX) has become the treatment of choice for end-stage liver disease (ESLD) and some cases of acute liver failure.

The liver performs many complex functions in the body, including glucose storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It is also the organ with a great capacity for regeneration. However, liver cirrhosis or acute intoxication results in serious damage of the liver tissue, which can lead to fatal complications, such as bleeding from the oesophageal varices, infections, refractory ascites, and encephalopathy that can progress to coma. For such patients, LTX is a life-saving procedure.

There are three types of surgical techniques: orthotopic (implantation and replacement of the diseased liver with the donor liver), heterotopic (addition of the donor liver while the diseased liver stays intact), and reduced LTX (a part of the living-donor liver put in place of the diseased liver). The procedure is extremely complex and requires excellent surgical technique and experienced anaesthesiologists.

Numerous advances in surgical techniques, better preoperative optimization of patients, intraoperative monitoring, and immunosuppression protocols have led to better transplantation results making LTX rather a safe procedure for the patients in whom it is performed.

Overall, one-year survival rate for deceased-donor LTX is over 85% whereas 10-year survival rate is up to 66% [3]. The main problem – rather a small number of liver donors – forced the development of alternative procedures, such as partial (living-related) LTX.

The purpose of this review was to give an overview of deceased-donor LTX indications and common procedures regarding perioperative management with the emphasis on the role of the anaesthesiologist in this procedure.

Discussion

Indications for Liver Transplantation
Selection of patients eligible for LTX is done by a hepatologist (gastroenterologist). They have to recommend LTX for patients with ESLD for whom all other treatment options are exhausted.

Indications for LTX include cirrhosis (whether viral or alcoholic), cholestatic disease, metabolic diseases, primary liver tumours, and acute hepatic failure due to intoxication.

The decision to list a patient for transplantation is based more on the severity of hepatic dysfunction than on the underlying aetiology. Priority is based on specific prognostic criteria using a number of scoring systems. The Child-Pugh score is used to determine the prognosis of the patient. The model for end-stage liver disease (MELD) indicates the required strength of treatment and the necessity of LTX.

Absolute contraindications for LTX are brain death, extra hepatic malignancy, active uncontrollable infection, active alcoholism and substance abuse, and severe cardiopulmonary disease.

Preoperative assessment
Most patients eligible for LTX have accompanying dysfunction of other organ systems besides hepatic disease. Preoperative assessment requires...
a multidisciplinary approach. It involves evaluation of hepatic dysfunction and associated complications as well as the concomitant diseases, and the patient’s motivation for the procedure as well as family support.

Cardiac evaluation
The assessment regimen varies between centres. As a minimum, an ECG and transthoracic echocardiography (TTE) should be performed in all patients.

Full functional assessment is often required for underlying coronary artery disease (CAD) and alcohol-related cardiomyopathy.

Incidence of CAD is 5% to 26% in patients undergoing LTX. Patients with risk factors such as diabetes, non-alcoholic steatohepatitis (NASH), previous CAD, and peripheral vascular disease need further evaluation.

Dobutamine stress myocardial perfusion imaging and dobutamine stress echocardiography (DSE) may assist in identifying patients with significant ischaemic heart disease, especially where exercise stress tests cannot be performed due to patient’s limited functional capacity.

The presence of coronary artery disease is associated with high mortality and morbidity (50% and 81%, respectively) during LTX, making DSE screening a routine preoperative test for adult transplant candidates in most centres.

Pulmonary evaluation
The pulmonary complications associated with liver disease include restrictive lung disease due to pleural effusions, intrapulmonary shunts, ventilation–perfusion (V/Q) abnormalities, and pulmonary hypertension.

Chest X-ray and pulmonary function tests may reveal pre-existing lung pathology. It is extremely important to recognize two syndromes which can lead to complications postoperatively: hepatopulmonary syndrome and portopulmonary hypertension.

Hypoxemia occurring in the absence of ascites or intrinsic lung disease is referred to as hepatopulmonary syndrome (HPS). This syndrome resolves after LTX and is characterized by intrapulmonary vasodilatation and V/Q abnormalities. However, the persistence of hypoxemia with 100% oxygen administration is considered to be a contraindication for LTX.

Approximately 3% to 4% of patients with ESLD presents with ‘portopulmonary hypertension’ (PPH). PPH is defined as a mean pulmonary artery pressure > 25 mm Hg or pulmonary vascular resistance > 120 dyne/s/cm5 in the presence of a normal pulmonary capillary wedge pressure. In severe PPH (> 45 mmHg) LTX is associated with increased perioperative mortality (> 70%) caused by right heart failure or hepatic failure.

Successful transplantation can be performed in such patients, but they have to be treated long-term with pulmonary vasodilators (inhaled NO or epoprostenol, a prostacyclin PGI2) to decrease pulmonary artery pressure.

These patients require additional haemodynamic monitoring perioperatively.

Renal evaluation
Renal function is an important predictor of survival for chronic liver failure and LTX.

Hepatorenal syndrome, with incidence of 13% to 40%, results in renal impairment and can lead to renal failure, and may require peritoneal haemofiltration. This syndrome resolves after successful LTX. Nephrotoxic antibiotics and contrast used for diagnostic studies should be avoided, if possible.

Neurological evaluation
The failure of hepatic clearance leads to an accumulation of toxins, such as ammonia and manganese, and to alterations in endogenous transmitters and messengers, including γ-aminobutyric acid (GABA), glutamate, and nitric oxide. The enzymes of the urea cycle are absent in the brain. The resulting accumulation of glutamine, an osmotic compound, targets the glial activities and results in cerebral oedema in acute liver failure. In chronic liver disease, compensatory changes affect for the absence of cerebral oedema.

Up to 80% of patients with acute liver failure develop cerebral oedema and increased intracranial pressure. Therefore, it is important to recognize these symptoms early to place additional monitoring, start adequate treatment, and avoid serious neurological impairment.

In chronic liver failure, the presence and staging of encephalopathy is required. Treatment of encephalopathy traditionally includes lactulose, non-resorptive antibiotic for selective gut decontamination and protein low nutrition.

Fluid and electrolyte disturbances
Hyponatraemia is commonly associated with portal hypertension and ascites as a result of water retention. A serum sodium < 125 mmol/L must be slowly and correctly corrected to reduce the risk of pulmonary oedema and central pontine myelinolysis. Hypoalbuminaemia, coagulopathy, and thrombocytopenia are not generally corrected preoperatively unless specifically indicated (e.g. active bleeding).

Gastrointestinal system
Oesophageal varices, portal hypertension, and ascites are frequently seen in ESLD patients.

Refractory ascites markedly impair the quality of life. These patients are forced to undergo frequent punctures and evacuation of ascites.

Delayed gastric emptying can be of major concern during the induction of anaesthesia.

Bleeding from varices requires immediate sclerotherapy and can
worsen the general condition of the patient, especially encephalopathy.

Another danger is the spontaneous bacterial peritonitis, which can ultimately lead to fatal infectious complications.

Endocrine system
Carbohydrate and protein metabolism is impaired. Glucose intolerance and insulin resistance occur often. Serum insulin levels increase due to hypersecretion and its decreased clearance.

Malnutrition is also common in advanced ESLD due to malabsorption, abnormal protein synthesis, and catabolism. These patients are subjected to complications and longer hospital stay.

Haematologic and coagulation system
All clotting factors, except von Willebrand factor, are synthesized in the liver. As a result, ESLD patients have low levels of all factors except fibrinogen, an acute phase reactant, and factor VIII. Decreasing levels of fibrinogen and factor VIII suggest the presence of primary fibrinolysis or disseminated intravascular coagulopathy (DIC). Prolonged prothrombin time correlates with the severity of liver disease and is one of the variables commonly used as a prognostic indication of perioperative risk.

Anaemia commonly occurs as a result of chronic disease, malnutrition, or bleeding.

Splenectomy decreases the number of circulating platelets and is the main cause of thrombocytopenia.

Intraoperative management
Drug metabolism
All plasma proteins, including albumin which mainly provides plasma oncotic pressure, are produced in the liver, except gamma-globulin. Decrease in albumin levels results in significant intra- and extra vascular volume changes, leading to increased volume of distribution of many drugs (i.e. neuromuscular blocking agents). The duration of action of some anaesthetics agents (such as opioids) is prolonged due to increased volume of distribution and decreased metabolism. ESLD patients may be resistant to some drugs due to increased binding to globulin. Hence, the initial dose of drugs is increased. Nevertheless, due to the decreased levels of albumin, the unbound fraction of these drugs is increased, leading to increased effect and duration of action of these drugs.

Premedication
Benzo diazepine premedication appears safe in most cases but it should be avoided in patients with hepatic encephalopathy. Premedication should also include anti-biotic and aspiration prophylaxis with proton pump inhibitor or histamine H2-receptor antagonist and metoclopramide. Mechanical thromboprophylaxis, in form of compressive leggins, is also advised unless contraindicated.

Positioning and operating room preparation
The patient is positioned supine with one or both arms abducted to a maximum of 70° to avoid brachial plexus injury. Different warming devices are used to maintain stable body temperature. Devices for rapid infusion of warm fluids and device for autologous transfusion (if applicable) are also used. Stat lab is advised due to frequent blood analysis.

Monitoring
Routine anaesthesia monitoring is applied before induction to general anaesthesia. Further, invasive cardiovascular monitoring may be established either pre- or post-induction, depending on the cardiovascular status and patient’s co-morbidities.

Haemodynamic monitoring is essential for successful liver transplantation. ESLD is characterized by high cardiac output state with decreased systemic vascular resistance and depleted intravascular volume. During different stages of LTX there are rapid and significant haemodynamic changes that need to be recognized promptly and wisely chosen haemodynamic monitoring is essential.

Various centres use different cardiac output monitoring. Most centres in Europe no longer use the pulmonary artery catheter (PAC or Swan Ganz catheter). New modalities for volume and cardiac status monitoring include increasing usage of transoesophageal echocardiography (TEE) intraoperatively. The use of less invasive cardiac output devices (i.e. arterial line pulse contour analysis – PICCO, LIDCO, and FloTrac/Vigileo) is continually increasing.

A nasogastric tube should be inserted with caution because of the possible injury of oesophageal varices and coagulopathy that may cause bleeding. Urinary catheter and temperature probe (oesophageal or rectal) are placed.

Patients with fulminant acute liver failure are at risk of raised intracranial pressure (ICP). They are generally transferred from ICU with ICP monitoring in situ. Conventional ICP monitoring is complicated by bleeding and infection without any survival advantage. Due to this fact many non-invasive methods, such as transcranial Doppler (TCD) or optic nerve sheath (ONSD) have been proposed for neurological monitoring. However, their use is still not widely accepted.

Induction and maintenance of anaesthesia
LTX is performed under general anaesthesia with endotracheal intubation and controlled mechanical ventilation. Patients presenting with significant ascites are at great risk for aspiration of gastric contents and therefore must undergo rapid sequence induction.
Careful monitoring and drug titrating is necessary to maintain cardiovascular stability.

Intraoperative ventilation with lower tidal volumes (6–8 ml/kg) and avoiding high positive end-expiratory pressure reduces decrease in preload and hence decreases the risk of bleeding\(^2\).

Maintenance of anaesthesia is achieved using a halogenated volatile agent (most commonly isoflurane, but sevoflurane and desflurane can be used) in an air–oxygen mixture, supplemented with an intravenous narcotic. Nitrous oxide is avoided to reduce cardiovascular depression, gut distension, and bubble formation if veno-venous bypass (VVB) is being used.

Commonly used opioids for intraoperative analgesia have no adverse effects on liver functions. However, there is the advantage of remifentanil with a very short context-sensitive half-life.

Muscle relaxation with atracurium or cis-atracurium is preferred because it provides adequate relaxation and reliable reversal after prolonged use due to its organ-independent elimination. Vecuronium bromide and rocuronium also provide optimal conditions but neuromuscular block must be closely monitored to prevent delayed recovery.

Epideral anaesthesia is not used because of the compromised coagulation and platelet function.

Fluid and blood component management

LTX surgery is associated with massive fluid shifts. Several large bore cannulae are required for rapid transfusion of blood and fluids, along with a 3–5 lumen central line. Where VVB is used, large cannulae are inserted percutaneously into an internal jugular and femoral vein. A rapid infusion system (i.e. Level 1) allows rapid transfusion of warmed fluids (37°C–38°C) at rates of up to 1500 ml/min.

The selection of various crystalloids during LTX should be based on their pH, electrolyte composition, osmolality, and metabolism. There is no ideal crystalloid solution and they all have limitation. Normal saline (0.9% NaCl) causes hyperchloremic acidosis while lactate in Ringers lactate requires liver metabolism for its elimination. Plasmalyte has a pH near normal and electrolyte and osmolality similar to plasma, but is proinflammatory and potentially cardiotoxic\(^11\).

The use of colloid rather than crystalloid as maintenance fluid reduces extravascular translocation of fluids, which results in less bowel oedema, improved mesenteric perfusion, and more rapid restoration of postoperative gut function. However, excessive colloid use (even modern low molecular weight hydroxy ethyl starches) may affect coagulation profile and increase the risk of renal injury\(^22\).

Albumins can be used due to the fact that these patients are often hypoaalbuminemic and hypovolemic.

LTX patients present with a wide range of coagulation profiles ranging from normal coagulation (hepatocellular carcinoma) to gross coagulopathy (fulminant hepatic failure). Protrombin time (PT) and activated partial thromboplastin time (aPTT) have been found to have a limited role in LTX as they measure only the procoagulant pathway without consideration for platelet function or fibrinolysis\(^23\).

Many centres use thromboelastogram (TEG), rotational thromboelastometry (ROTEM), or Sonoclot because they provide a detailed assessment of both pro- and anticoagulant status of the blood. Use of TEG and ROTEM has been found to reduce the transfusion requirements in LTX\(^24\).

Fresh-frozen plasma (FFP), cryo-precipitate and platelet infusions are administered, if required, in patients who are coagulopathic and require correction of their coagulopathy. Red cells are not transfused unless the haematocrit falls below 25%, except in patients with known coronary or cerebrovascular disease. This haematocrit value allows adequate oxygen delivery but prevents hepatic artery thrombosis.

The introduction of cell salvage techniques for re-transfusion has also decreased blood transfusion requirements. Contraindications include malignant aetiology and infected ascites.

Monitoring of full blood count, clotting, electrolytes and blood gases is carried out hourly or as clinically indicated. This data guide the management of ventilation, calcium and potassium supplementation, glycaemic and acid–base management, and blood replacement therapy.

Surgery

Majority of LTX was done in an orthotopic technique. It can be done by using veno-venous bypass (VVB) or by 'piggyback' technique which preserves the recipient's vena cava.

LTX involves the following three phases: pre-anhepatic, anhepatic, and post-anhepatic or neohepatal phase.

Phase I (pre-anhepatic phase)

This phase involves dissection and mobilization of the liver. Haemodynamic instability may be seen as a result of surgical manipulation: drainage of litres of ascites upon incision, transection of large varices, and manipulation of the liver that temporarily obstructs venous return. The risk of an air embolism during the manipulation of vena cava should be considered in case of sudden decrease in expired carbon dioxide associated with haemodynamic instability.

In this period of liver transplantation, the primary issue is surgical bleeding. Fluid resuscitation results in a decrease of coagulation factors and platelet count. Packed red cells and fresh frozen plasma should be
prepared at this time. Nevertheless, as a result of improved intraoperative techniques, requirements for blood products have been reduced over the last decade.\textsuperscript{25}

**Phase II (anhepatic phase)**

It starts with the occlusion of blood inflow to the liver. The graft is set in the patient’s body and the venous Anastomoses are completed. The clamping of the inferior vena cava and portal vein and division of hepatic vasculature results in the loss of venous return leading to a high risk for cardiovascular collapse with a marked decrease in cardiac output and hypotension. The resulting increase in distal venous pressure may increase bleeding, impair renal perfusion, and often promote oedema and ischaemia of the intestines.

Veno-venous bypass (VVB) can be used to improve haemodynamic stability, reduce blood loss, and maintain intraoperative renal function and cerebral perfusion pressure in patients with acute fulminant failure. However, the use is not risk-free and can be accompanied by air embolism and thromboembolism. Other side effects include hypothermia, haematoma, and vascular and nerve injury as a complication of catheter placement, wound infection, or dehiscence, and prolonged operative and warm ischaemia time.

The decision for VVB use depends on the experience of the medical team, its preferences and judgement. During this phase, no haemostatic techniques are produced, fibrinogen is deficient and anti-thrombin concentrations decrease, leading to worsening of coagulopathy and the onset of fibrinolysis. Thrombocytopenia can aggravate due to massive blood transfusion and platelet consumption. Fibrinolysis may be prevented or attenuated by antifibrinolytic agents, such as aprotinin and tranexamic acid.\textsuperscript{26}

Absent citrate and lactate metabolism results in progressive acidosis. Hypocalcaemia and hypomagnesaemia must be treated to prevent coagulopathy and cardiac depression.\textsuperscript{27}

**Phase III (post-anhepatic or neohepatal phase)**

When the venous anastomoses of the graft are completed, the liver is reperfused with blood. Afterwards, the arterial and biliary anastomoses are formed. Before reperfusion, methylprednisolone (500 mg) is also given as a slow IV infusion as part of immunosuppression protocol and as protection against ischaemia-reperfusion injury.

This reperfusion of the graft is associated with elevations of potassium and hydrogen ion concentrations, increase in preload, and decrease in systemic vascular resistance with a decrease in blood pressure.

Serum potassium concentrations must be checked periodically (numerously), especially in the first 15 minutes after reperfusion. Hyperkalaemia must be aggressively corrected because it can lead to malignant arrhythmias and cardiac arrest.

Reperfusion can result in myocardial depression presenting as post-reperfusion syndrome (PRS) defined as at least 30\% decrease in mean systemic blood pressure for more than 1 min during the first 5 min following reperfusion.\textsuperscript{27} Its aetiology is multifactorial and can include acute acidosis, hypercalcaemia, hypothermia, and other cellular mechanisms.

Reperfusion complications may be diminished by use of the piggy back technique contributing to a side-bite inferior vena cava allowing the venous return to continue.\textsuperscript{28} During this phase, patients often require vasopressor or inotropic support.

Functioning graft takes up increased potassium. Metabolic acidosis begins to correct with restoration of lactate metabolism and bicarbonate production. Primary non-function or delayed function of the graft (up to 10\% of cases) is indicated by ongoing metabolic acidosis, coagulopathy, and absence of bile production. Most cases require urgent re-transplantation. Ischaemia reperfusion injury is associated with primary graft dysfunction and delayed graft function. Numerous strategies have been proposed for prevention of this injury and include ischaemic preconditioning and pharmacological management with N-acetyl cysteine, sevoflurane, or remifentanil in animal model. Their clinical use has yet to be determined.

**Postoperative care**

Early extubation is possible in most patients with good graft function. This has shown to improve graft function, reduce duration of stay in the ICU, and reduce incidence of nosocomial infections.\textsuperscript{29}

Patients after LTX have limited analgesic options due to graft function. Acute postoperative pain is treated with opioids (hydromorphone, fentanyl, tramadolum), which have to be titrated and closely monitored to avoid adverse effects. Moderate pain can be cautiously treated with NSAIDs, because of the risk of acute renal failure and paracetamol (acetaminophen) appears to be safe in a maximum dosage of 2 to 3 g/day.\textsuperscript{30}

The function of the transplanted graft is closely monitored with laboratory findings (which show the degree of ischaemia reperfusion injury and liver synthetic function), and Doppler ultrasound (which monitors the functioning of vascular anastomosis, and potential development of haematoma, bilia leak, etc.).

The use of immunosuppressive therapy is essential. It starts on the first postoperative day in the ICU and continues later under the surveillance of hepatology specialists. Protocols vary among medical centres. However, most liver transplant recipients receive corticosteroids plus a calcineurin inhibitor, such as tacrolimus or cyclosporine, plus a purine antagonist, such as mycophenolate mofetil. If the patient has a co-morbidity, patients with good graft function.

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such as active hepatitis B, high doses of hepatitis B immunoglobulins are administered. The risk of chronic rejection in liver transplants decreases over time so the level of immunosuppression can be reduced.

Therapeutic support, including antibacterial, antiviral, antifungal prophylaxis, as well as the thromboembolic and ulcer prophylaxis, is also required.

Conclusion

LTX has evolved over the years. Survival is still increasing gradually in relation to greater expertise in the surgical procedure and management of immunosuppressive therapy. Still, further studies are needed in areas of haemodynamic monitoring, and blood and coagulation management to prove its efficiency.

Patients undergoing LTX have severe liver disease characterized by multisystem disorders that provide many anaesthetic challenges. A detailed monitoring of the patient and a careful therapeutic concept is required to meet the extraordinary conditions during this exciting adventure called liver transplantation.

Abbreviations list

CAD, coronary artery disease; DIC, disseminated intravascular coagulopathy; DSE, dobutamine stress echo; HPS, hepatopulmonary syndrome; PRS, postreperfusion syndrome; PPH, portopulmonary hypertension; VVB, transthoracic echocardiography; VVT, veno-venous bypass.

References