

## Anesthesia in Liver Transplantation

Meral Kanbak<sup>1</sup>, Ayse Heves Karagoz<sup>1</sup> and Filiz Üzümçügil<sup>2</sup>

<sup>1</sup>Hacettepe University School of Medicine,

Department of Anesthesiology and Reanimation, Ankara,

<sup>2</sup>TCSB Ankara Etlik Zübeyde Hanım Maternity and Women's Health Clinic  
Teaching and Research Hospital, Department of Anesthesiology and Reanimation Ankara,  
Turkey

### 1. Introduction

Liver transplantation, is the replacement of unhealthy liver with a new liver allograft. This surgical procedure is now widely common all over the world in various medical centers. The major limiting factors of this surgery is the lack of available donors and decreased chance of appropriate patient selection. Anesthetic management of organ donors includes intensive management of heart beating and brain dead donors; however the augmentation of waiting list for liver and inadequate cadaveric organs resulted in elevated living donor transplantation rates especially for the critically ill patients who will not survive waiting until a brain dead donor is provided, resulting in the growing experience in anesthetic techniques for the management of living donors (Pickett et al, 1994; Lutz et al, 2003).

The most common indications for orthotopic liver transplantation (OLT) in adults are alcoholic cirrhosis, chronic cirrhosis due to hepatitis C, primary biliary cirrhosis and primary sclerosing cholangitis. The most common indication for OLT in pediatric patients is biliary atresia, followed by metabolic disorders (alfa-1 antitrypsin deficiency, Wilson's disease, tyrosinemia, Crigler-Najjar type-1 syndrome), fulminant hepatic failure, cryptogenic cirrhosis, neonatal hepatitis, and malignancy.

The association of liver failure with pathologic status of all other organ systems requires a thorough examination of the liver host and a fastidiously scheduled anaesthesia. A detailed monitoring of the patient and a careful therapeutic concept is required to meet the extraordinary conditions during liver transplantation. This report sheds light on the anaesthesiological approach of the liver transplantation and summarizes suitable therapeutic options.

### 2. Anesthetic management of the living donors

In order to permit successful transplantation of the liver, it is necessary to provide excellent conditions for the donor while preserving optimal hemodynamic parameters (Pickett et al, 1994; Lutz et al, 2003). However anesthetists may face severe hemodynamic instability, which is frequently seen in donors especially during the harvesting period when organs are removed (Pickett et al, 1994). Hemodynamic stability can be achieved by maintaining

sufficient organ perfusion, adequate cardiac output, avoiding excessive bleeding, keeping hematocrit at about 30% and preventing coagulopathies (Lutz et al, 2003).

Invasive monitoring is obligatory to ensure sufficient organ perfusion and cardiac output, because of the major hemodynamic, hematologic and metabolic disturbances associated with hemorrhages and electrolyte imbalances that may be seen especially in right hepatectomy procedures (Lutz et al, 2003). During the operation, a central venous pressure (CVP) below 5 cm H<sub>2</sub>O is suggested in many liver transplantation protocols to decrease blood loss and graft edema. Chen et al. found a correlation between CVP and blood loss during resection of liver; however, Chhibber et al. reported no significant decrease in blood loss in patients with low CVP (Chen et al, 2000; Chhibber et al, 2007). Balci et al. has recommended an acute intraoperative normovolemic hemodilution technique and fluid restriction in a group of live donors (Balci et al, 2008).

The type of the intravenous solutions are also important in liver transplantation as well as their amount. Although there is no definitive data about a detrimental effect, 0.9% saline is known to be associated with hypercloremic metabolic acidosis. The Ringer's lactate solution is contraindicated because lactate metabolism will be disrupted as the liver is resected, furthermore serum lactate levels increase after resection. Plasmalyte may be an alternative being devoid of lactate, however there is no clear data that it is superior to other crystalloids. Despite the absence of definitive data about adverse outcome, since hydroxyethyl starch solutions are known to effect the coagulation system, they should be used with caution. 5% albumin can be used after hepatectomy, but it has also no proven benefit (Hwang and McCluskey, 2010).

Preventing major life threatening bleeding during transsection of liver requires extraordinary attention by the surgical team. Preparation of autologous blood and hemodilution in operating room may prevent transfusion complications (Merritt et al, 2004).

Anesthetic management of living donors is maintained with general anesthesia. Commonly used anesthetic agents such as modern inhalational anesthetics, sufentanil, fentanyl, remifentanil, propofol, cis-atracurium and vecuronium have no adverse effects on liver functions. In live donor hepatectomies, Rabie et al. investigated the effects of propofol or isoflurane, both of which were similar in terms of perioperative hemodynamics, blood loss, duration of surgery and hospital stay (Rabie et al, 2006).

Appropriate antibiotic prophylaxis (at least 20 minutes before skin incision) including a third-generation cephalosporin and metronidazol covering anaerobic infections, in addition to venous thromboembolism prophylaxis including subcutaneous heparin or low-molecular weight heparin with pneumatic compression stockings should be administered. Prior to donor graft perfusion 1000-5000 IU intravenous heparin is administered and its reversal is often not needed (Hwang and McCluskey, 2010).

Considering the rapid recovery from anesthesia and difficulties in pain control, general anesthesia combined with epidural anesthesia seems to be effective; a mid thoracic epidural application may be the best form of pain relief during early postoperative period. However, despite the data that epidural analgesia seems to be safe in spite of postoperative coagulation disorders in hepatectomy operations (Choi et al. 2007), it has been discouraged because of postoperative unpredictable coagulation profile and epidural hematoma risk of

living donors (Stamenkovic et al, 2011). On the other hand, since the kinetics of intravenous analgesics and opioids after liver resection have not been clarified yet, extra attention is required for the usage of these agents. Hwang and McCluskey reported that intravenous patient-controlled analgesia or intrathecal morphine may become an alternative for pain control in living donors. Regional techniques such as paraspinal blocks, transversus abdominus plane blocks, incisional field blocks are still investigated for their effect and safety in these patients (Hwang and McCluskey, 2010).

### 3. Anesthetic management of the recipients

Once the patient is scheduled for liver transplantation, the transplantation team has to consider the deterioration in the recipient functional status. All members of team, especially anesthesiologists should do their best to reduce the morbidity and mortality of this procedure in such high risk patient population.

#### 3.1 Preoperative evaluation and premedication

The selection of appropriate and perfectly prepared recipient is the gold standard for the success of liver transplantation. Besides the complexity of the operation, most patients have an already disturbed physiology because of the hepatic disease, challenging the anesthesiologist (Table 1) (Findlay, 2002). Liver diseases strike all major organ systems leading to an unexpectedly chaotic scenario for the anesthesiologist, including hepatic failure, multiorgan dysfunction, encephalopathy, and severe metabolic disorders, and revealing the preoperative evaluation and premedication an essential part of the preparation of the patient. Besides, sepsis, metastatic malignancy, severe congestive heart failure, pulmonary hypertension and unresolved alcoholism are the contraindications for liver transplantations.

**Cardiovascular system:** Since the criteria for transplantation is expanded, the age limits has been extended to the older ages, thus bringing ischemic heart diseases as a major problem to be evaluated in the preoperative period (Steadman, 2004). Although coronary angiography is the gold standart for this assessment, considering the usage of radiographic contrast in a patient group with a high-risk of renal dysfunction precludes the usage of this technique; leading to other screening methods such as transthoracic echocardiography in combination with a stress test. Exercise tests are not suitable for end-stage liver disease patients, because they cannot complete the test adequately. Thus, pharmacologic stress tests; stress echocardiography or myocardial perfusion scan have to be used instead (Niemann, 2010). Dobutamine stress echocardiography (DSE) is the screening method in many centers; including the advantage of diagnosing pulmonary hypertension and valvular heart disease (Niemann, 2010; Steadman, 2004). Preoperative assessment should include echocardiography in order to determine the baseline cardiac function and pulmonary artery pressures (Findlay, 2002). In alcoholic liver disease, amyloidosis, hemochromatosis and Wilson's disease nonischemic cardiomyopathy may be seen. However hypertrophic cardiomyopathy is rarely seen, it may cause dynamic left ventricle outflow tract obstruction during liver transplantation (Aniskevich et al, 2007). Most of the end-stage liver disease patients have a hyperdynamic state characterised by an increased cardiac output and arteriolar vasodilatation (Glauser et al, 1990). Portopulmonary hypertension may be found in these patients. Severe

| System  | Patophysiologic changes related to liver failure  |  |
|---|---|--|
| Cardiovascular                                    | <ul style="list-style-type: none"> <li>Hyperdynamic Circulation</li> <li>Portopulmonary Hypertension</li> </ul>   | <ul style="list-style-type: none"> <li>High cardiac output,</li> <li>Low resistance,</li> <li>Increased cardiac index and left atrial size,</li> <li>Mild left ventricular hypertrophy and ischemic heart disease; clinical cardiomyopathy (especially alcohol, amyloid, Wilson's hemochromatosis);</li> <li>Autonomic neuropathy (mild in cirrhosis, moderate in amyloid)</li> </ul>  |
| Respiratory                                       | <ul style="list-style-type: none"> <li>Hypoxia</li> </ul>   | <ul style="list-style-type: none"> <li>Restrictive pattern (ascites),</li> <li>Pleural effusion;</li> <li>Flow-related or anatomical intrapulmonary shunting (hepatopulmonary syndrome);</li> <li>Non-cardiogenic pulmonary edema (fulminant hepatic failure);</li> <li>Obstructive airways disease (especially cystic fibrosis, alpha-1 anti-trypsin deficiency);</li> <li>Interstitial lung disease (primary biliary cirrhosis)</li> </ul> |
| Hematologic                                       | <ul style="list-style-type: none"> <li>Coagulopathy</li> <li>Anemia</li> </ul>  | <ul style="list-style-type: none"> <li>Decreased and defective synthesis of Vit K dependent clotting factors,</li> <li>Trombocytopenia (hypersplenism or marrow depression),</li> <li>Platelet dysfunction;</li> <li>Low grade DIC and/or hyperfibrinolysis</li> </ul>   |
| Central Nervous System                            | <ul style="list-style-type: none"> <li>Hepatic encephalopathy</li> <li>Cerebral edema (fulminant failure)</li> </ul>  |  |
| Renal System, Electrolyte and Metabolic disorders | <ul style="list-style-type: none"> <li>Hepatorenal Syndrome (prerenal failure from splanchnic 'steal');</li> <li>Acute tubular necrosis from sepsis;</li> <li>Tacrolimus/cyclosporin-related renal impairment; renal tubular acidosis</li> <li>Hyponatremia</li> <li>Hypomagnesemia,</li> <li>Hyperkalemia,</li> <li>Hypokalemia, and/or metabolic acidosis and hypoglycemia</li> </ul> |  |

Table 1. Patophysiologic changes related to liver failure (Findlay, 2002; Ozier &amp; Klinck, 2008)

portopulmonary hypertension is associated with increased perioperative mortality and right heart failure (Krowka et al, 2000; Ramsay et al, 2000). For detecting preoperative portopulmonary hypertension, transthoracic echocardiography may be reliable enough in experienced hands, but echocardiography should be reperformed.

**Respiratory system:** Respiratory complications seen in liver disease include restrictive lung disease, intrapulmonary shunts, pulmonary hypertension and ventilation-perfusion abnormalities. Hypoxemia is often related to the restrictive lung disease caused by ascites and/or pleural effusions, frequently responding to fluid removal. However, hypoxia may occur in the absence of ascites or intrinsic pulmonary disease, then this is called hepatopulmonary syndrome; contributing to shunting ventilation-perfusion mismatch and/or diffusion defects. The presence of pulmonary hypertension responding to vasodilators is not a contraindication for transplantation. Pulmonary hypertension may improve, persist or develop following transplantation (Steadman, 2004).

**Hematological system:** In addition to the routine blood tests; coagulation tests and arterial blood gases should also be obtained (Findlay, 2002). In the normal hemostasis, liver is important for the production of prothrombin, fibrinogen, factors V, VII, IX and X (except von Williebrand factor-synthesized in endothelial cells), synthesis of antithrombotic modulating factors (protein S, protein C and antithrombin III) and components of fibrinolytic system (plaminogen and  $\alpha_2$ -antiplasmin); also the clearance of activated coagulation factors. As the liver function is impaired, this natural balance between coagulation and its inhibition is impaired, whereas the balance between the fibrin polymerization and fibrinolysis is also disturbed; which occurs due to the decreased production of antiplasmin and inadequate clearance of tissue plasminogen activators, (Hannaman&Hevesi, 2011). All the coagulation factors are decreased, except fibrinogen and factor VIII. Besides, Fitzgerald factor, alpha-1 antitrypsin, alpha-2 macroglobulin, antithrombin-III and plasminogen levels are all decreased. Fibrin degradation products are positive in one third of the patients. Thrombocytopenia occurs in 70% of the patients, often complicated with the functional derangement of the platelets. For the best approach to treat coagulopathic disorders, defects must be identified in laboratory screening tests to predict bleeding risk in recipients, but the liver diseases have complicated effects on the balance between prohemostatic and antihemostatic mechanisms. Prothrombin time (PT), the activated partial thromboplastin time (APTT) and platelet count shows the defect in procoagulant functions. Unfortunately, defects in inhibitory pathways are less clear. The net effect of instability of these systems is unpredictable and administration of fresh frozen plasma (FFP), platelets and other blood products before the surgery should be reconsidered. There is a correlation between the severity of preoperative coagulopathy and intraoperative requirement for blood and blood products; as the severity increases, requirements are increased. Chronic disease anemia, malnutrition and bleeding is also common in recipients. In patients with the coagulation disorders intramuscular injections should be avoided.

**Central nervous system:** In advanced liver diseases, hepatic encephalopathy within a range of mild stupor, deep coma and unresponsiveness, is often seen. Diuretic therapy, gastrointestinal bleeding, infections and advancement in liver disease worsen encephalopathy. In order to exclude a preexisting organic disease mimicing hepatic encephalopathy, EEG, stimulated potential tests and computed tomography are recommended to be performed.

Any organic disease, that contributes to the changes in cerebral functions, is a contraindication for liver transplantation. Cerebral edema occurs in 50% of the patients with acute fulminant hepatitis. Cortical atrophy and non-specific changes are also seen at variable degrees in patients with chronic liver disease. Chronic liver disease is rarely associated with cerebral edema, but hepatic clearance failure leads to accumulation of toxins and alterations in endogenous transmitters, messengers such as  $\gamma$ -amino butyric acid (GABA), glutamate and nitric oxide. In preencephalopathic patients benzodiazepines should be avoided. In fulminant liver failure with Grade III-IV encephalopathy intracranial pressure monitoring may be required in order to maintain cerebral perfusion pressure  $>60$  mmHg (Ozier&Klink, 2008). A severe coagulopathy may result in intracranial hemorrhage.

**Renal system:** The most common cause of renal failure associated with hepatic failure is hepatorenal syndrome, which is characterized by the absence of primary renal disease, proteinuria, hypovolemia and hemodynamic cases of renal hypoperfusion. Treatment with vasoconstrictors improving splanchnic vasodilation, decreasing endogenous vasoconstrictors leading to an improvement in renal blood flow is often successful (Duvoux, 2002; Gines, 2004; Wong, 2004). Contrast for diagnostic procedures and nephrotoxic agents should be avoided in these patients. Even a less advanced renal disease deserves management because it may also worsen the posttransplant period (Davis, 2002).

**Gastrointestinal system:** Esophageal varices, portal hypertension, ascites are frequently seen in patients with end-stage liver-disease. This complex state also includes delayed gastric emptying which contributes to a major problem especially during the induction of the anesthesia, thus premedications should include "aspiration" prophylaxis with ranitidine, metoclopramide, and particulate-free antacid.

**Endocrine system:** In liver diseases it is widely known that the carbohydrate and protein metabolism is impaired, and glucose intolerance and insulin resistance occur. Serum insulin level is increased both because of the hypersecretion and decreased clearance. In addition to this, in acute fulminant hepatitis, depletion of glycogen stores, decreased gluconeogenesis and other humoral changes may result in a severe hypoglycemia. In advanced liver diseases, severe reductions in albumin levels may also be seen ( $<2$ gr).

**Drug metabolism:** All the plasma proteins, especially albumin which mainly provides plasma oncotic pressure, are produced in liver, except gamma-globulin. The decrease in albumin levels ( $<2$ gr) results in intra- and extravascular volume changes, leading to an increase in distribution volume of drugs (e.g. neuromuscular blocking agents). Also, the duration of action of some anesthetic agents (such as opioids) are prolonged because of the increased volume of distribution and decreased metabolism. End-stage liver disease patients may be resistant to some drugs due to increased binding to globulin. Thus, initial dosages of the drugs are increased; on the other hand, because of the decreased levels of albumin, the unbound fraction of the drugs is increased; which leads to increased effectiveness and duration of action of these drugs.

**Premedication** is usually administered unless the patient has an advanced hepatic encephalopathy. Oral diazepam 5-10 mg, lorazepam 2-3 mg can be used for adult patients, whereas 0.1-0.2 mg/kg of diazepam can be used orally for pediatric group of patients. Intramuscular injections should be avoided in patients with coagulopathy. Low dose midazolam (1-2 mg/kg) has become a routine before induction in the anesthetic practice.

All patients should be considered to have full stomach; H<sub>2</sub> receptor blockers and particulate-free antacids can be used preoperatively.

### 3.2 Monitoring

Routine monitoring consisting of electrocardiography, pulse oximetry, capnograph and temperature monitor should be in place (Findlay, 2002). Full invasive monitoring including direct arterial blood pressure (close monitoring of the systemic pressures, also facilitating frequent blood sampling) (Peterfreund and Allain, 2003), central venous, and pulmonary artery pressure measurements are obligatory for the management of severe coagulopathy, metabolic disorders, massive blood loss, temperature alterations, hemodynamic instability, and other organ dysfunctions (Table 2).

| Monitoring                         |
|------------------------------------|
| • ECG                              |
| • Pulse Oximetry                   |
| • Capnography                      |
| • Temperature                      |
| • Arterial Catheter                |
| • Central Venous Catheter          |
| • Pulmonary Artery Catheter        |
| • Transesophageal Echocardiography |

Table 2. Monitoring during liver transplantation (Findlay, 2002; Peterfreund and Allain, 2003)

**ECG:** ECG monitoring is a cornerstone showing clinical outcome of electrolyte changes. Due to the rapid and profound changes in electrolyte levels during the various phases of liver transplantation, ECG may reflect the cardiac disturbances; which require prompt treatment. Fatal ventricular fibrillation due to the hyperkalemia during reperfusion period has also been reported (Ozier & Klink, 2008).

**Arterial blood pressure:** Invasive arterial blood pressure monitoring is essential for providing continuous monitoring to see frequent hemodynamic changes usually secondary to surgical manipulations such as caval clamping, sudden blood loss, hepatic reperfusion during liver transplantation and also providing access for blood sampling for coagulation tests. Radial artery pressure monitoring may underestimate aortic pressure in hypotensive scenarios and femoral arterial systolic pressure is higher than radial, and the use of vasoconstrictors increases these variances (Arnal et al, 2005).

**Central venous cannulation and pulmonary artery catheterization:** Pulmonary artery catheterization (PAC) and CVP monitoring are standards in many centers. Liver transplant recipients are hyperdynamic, characterized by increased cardiac output (CO) and decreased peripheral vascular resistance (SVR) and arterial pressure (Liu et al, 2006; Moller & Henriksen, 2008). The patients with cirrhosis have a reduced total blood volume index (Henriksen et al, 1989), because of this relative hypovolemia, adequate volume management during liver transplantation is a gold standard for improvement of tissue perfusion (Nasraway et al, 1995). The various phases of liver transplantation may limit the accuracy of CVP measurements, however considering the low CVP approach to reduce blood loss and

liver congestion, central venous cannulation is necessary (Niemann, 2010). Central venous cannulation can be applied before or after anesthetic induction and endotracheal intubation. However, the patients with encephalopathy, tense ascites, respiratory compromise caused by atelectasis or pleural effusions, may not tolerate the Trandelenburg position and draping of the face that are required for the central cannulation; thus it may be more suitable performing these procedures after the induction of anesthesia (Peterfreund and Allain, 2003). Although less invasive monitoring gets more popular nowadays, because of severe PAC-induced ventricular arrhythmias (Gwak et al, 2007); PAC may still be particularly useful in renal insufficiency, respiratory compromise or unstable hemodynamics that exist prior to surgery (Peterfreund and Allain, 2003).

**Transesophageal echocardiography:** Transoesophageal echocardiography (TEE) is increasingly used for cardiac monitoring. It is relatively noninvasive and provides visual information on valvular and ventricular function and gives a chance of diagnosis of embolization, but unfortunately it is not available in many centers (Burtenshaw et al, 2006). In a report of multi transplant centers the rate of PAC and TEE used was respectively 30% and 11.3% (Schumann et al, 2003). During the last decade, transpulmonary thermodilution has been becoming popular to measure circulating blood volumes (Shippy et al, 1984). In recent years, noninvasive techniques such as lithium thermodilution is compared with PAC (Costa et al, 2008). Vigileo monitor is a good choice at low and normal CO, but is not appropriate for the hyperdynamic cirrhotic patients (Della et al, 2008; Biancofiore et al, 2009; Biais et al, 2008) (see also Future Directions for Circulatory Monitoring).

**Temperature:** Large incisions and prolonged duration of the procedure result in a high risk of hypothermia; to prevent the heat loss warming devices, heated humidifier, warming blanket, and a forced-air warming device should be present (Findlay, 2002).

**Venous access:** Sufficient large-bore venous access should be in place in case of a sudden, massive hemorrhage. Since the procedure involves inferior vena cava (IVC) obstruction; the cannulas should be in the upper part of the body. This venous access is also needed for the return of blood if veno-venous bypass (VVB) is used. Peripheral or central often two 8F or larger cannulas are preferred. A rapid infusion pump should be ready to infuse blood or fluids warmed to 37°C at a rate of 1.5L/min (Findlay, 2002).

**Other monitors:** All patients have nasogastric tubes and bladder catheters (Peterfreund and Allain, 2003). Nasogastric tubes should be used with caution because of the possible esophageal varices and coagulopathies that may cause bleeding (Topal & Celik, 2009).

**Future directions for circulatory monitoring:** A perfect monitoring device for circulation has not been clearly defined yet. There are ongoing investigations for continuous hemodynamic monitoring such as the FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA, USA), which is a self-calibrating arterial pulse contour cardiac output monitoring system; and LiDCO (LiDCO Cardiac Sensor System, London, UK) which is a pulse contour waveform analysis system. However, because of the various changes in hemodynamics during phases of liver transplantation, these monitors lose their accuracy. Similarly, thermodilution technique may also become inaccurate because of the rapid changes in temperature, rapid infusion of fluids and changes due to reperfusion of the graft. It is difficult to recommend one monitor as a superior to the other, so while planning monitoring, one of the devices including PAC, CVP and TEE is going to be chosen in addition to arterial line or lines

(sometimes two arterial lines are preferred) (Liu et al, 2011). As the correlation between the pathophysiology of hepatic microcirculation and ischemia/reperfusion injury has been demonstrated, intraoperative analysis of ischemia/reperfusion-induced impairment of hepatic microcirculation has gained interest. Orthogonal polarization spectral imaging has been used accurately for this purpose; quantifying the sinusoidal perfusion rate, vessel diameter and venular RBC velocity (Puhl et al, 2005).

### 3.3 Anesthetic induction and maintenance

Drug metabolism and clearance depend on the state of liver blood flow and P450 cytochrome system in hepatocytes. Due to the various disease states with different patterns of liver dysfunction, there is not a standard protocol for any drug. Drug biotransformation is related to the anesthetic practice in two ways. One of them is the sensitivity to the microsomal enzyme induction accelerates the biotransformation; the inhalational anesthetic agents and barbiturates cause microsomal enzyme induction. The second one is the impairment of hepatic blood flow in hepatic diseases leading to an increase in half-lives of drugs, because of the decrease in their biotransformation rates. In advanced liver diseases, the half-lives of meperidine, lidocaine and diazepam have been shown to be increased, similar to the duration of action of thiopental. In healthy patients thiopental binds to protein at a rate of 75%, while 50% in liver diseases. Thus, considering the decrease in metabolism and protein binding of the drugs in these patients, it should be kept in mind that intermittent dosing and usage of different drugs as combinations may result in accumulation of these drugs, which is very important in anesthetic practice.

Careful monitoring of drug effects with titrating the drug, considering the coagulation profile, volume status, and general hemodynamic state of patients, is important for clinicians to be current in their understanding of how transplant patients should be managed.

After preoxygenation, the induction of anesthesia may be performed by using either one of the hypnotic agents, thiopental or ketamine using invasive monitoring, and also midazolam can be used for its amnestic properties and minimal effects on hemodynamics. A routine rapid sequence induction with cricothyroid pressure should be performed because of the risk of aspiration. A semi-upright position can be applied until the abdomen is open; in order to prevent rapid oxygen saturation and to facilitate ventilation. Liver failure associated with renal dysfunction with increased potassium levels may prevent the usage of succinylcholine (Peterfreund and Allain, 2003). The pharmacokinetic changes, increase in extracellular volume, decrease in serum albumin and glycoprotein levels and elevated bilirubin and other metabolites in liver disease; result in an increase in the requirement of first dose of non-depolarizing muscle relaxants and prolong the duration of their action. Because of the organ-independent elimination and diminished histamine release cis-atracurium and atracurium are preferred; however, the others can also be used safely (Topal&Celik, 2009); vecuronium bromide and rocuronium as neuromuscular blocking agents provide optimal conditions. The new liver graft may be evaluated by vecuronium since the time for the return of a train-of-four (TOF) with a nerve stimulator correlates with the function of the new liver (Lukin et al, 1995). Similarly, the duration of action of rocuronium is also used for the assessment of allograft function; >150 minutes refers to allograft dysfunction (Marcel et al, 1997).

In the intraoperative period; using lower tidal volumes (6-8 ml/kg) and avoiding positive end-expiratory pressure may lower the preload and decrease the risk of bleeding (Hannaman&Hevesi, 2011). Different variations have been used for anesthesia maintenance and all have been informed to have less side effects on liver functions (Adachi et al, 2003). Maintenance of anesthesia can be provided by using isoflurane, desflurane or sevoflurane (Lukanovic et al, 2008) in an air-oxygen mixture with their minimal metabolism in the liver, supplemented with sufentanil or remifentanil infusions. Isoflurane has been the volatile agent to be preferred because of its vasodilation effect on hepatic circulation, which is advantageous for the reperfused graft, preserving splanchnic blood flow better than the others; especially when it is compared to the vasoconstrictor effects of halothane. Investigations addressing the effects of desflurane has conflicting results. In an animal study it has been shown to decrease hepatic blood flow in a dose dependent manner at concentrations up to 1 MAC; however in a human study although excluding patients with hepatic diseases and the results were not significant, it has been shown to provide better hepatic blood flow compared to that of isoflurane. In another study comparing the effects of desflurane and sevoflurane in terms of hepatic blood flow and hepatocellular integrity; both agents well preserved the hepatic functions, but decreased the splanchnic perfusion and oxygen delivery to the liver disturbing the hepatocellular integrity and gastric tonometry. The increased metabolism of sevoflurane which is a hundred times that of desflurane is not known to cause a detrimental effect on the liver (Steadman, 2004). In one of our study, we investigated the effects of sevoflurane in terms of metabolism and renal functions in liver transplantation, and sevoflurane seemed to have minimal effects on the kidney during liver transplantation (Kanbak et al, 2007). Erdem et al. reported a case of liver transplantation for the effects of sevoflurane in terms of extrahepatic metabolism and possible nephrotoxicity in liver disease; revealing a correlation between the levels of N-acetyl glucosaminidase excretion and urine fluoride levels and no impairment in serum BUN and creatinin levels (Erdem, 2006). In fulminant hepatic failure, due to the elevated intracranial pressure, volatile anesthetic agents should be avoided or used with caution at lower dosages combined with ICP monitoring (Steadman, 2004). As an intravenous anesthetic agent propofol is another good alternative. Takizawa et al. found that during the anhepatic phase, compared with the dissection phase, the clearance of propofol was decreased and afterwards liver allografts immediately metabolized propofol (Takizawa et al, 2005). Morphine and propofol which rely on conjugation pathway may be more tolerated (Brown et al, 1993).

Rossaint et al. combined early postoperative extubation and restrictive intraoperative fluid management techniques in liver transplant recipients (Rossaint et al, 1990). This approach resulted in rapid recovery of new liver functions and favoured early extubation. Early extubation is a goal for the operating team, because early liver graft recovery is associated with early patient recovery. Postoperative mechanical ventilation following liver transplantation is not required nowadays in the majority of patients, since immediate postoperative extubation is usually safe and well tolerated. In poor clinical condition with severe preservation injury, special attention is required in extubation. These patients may not be appropriate for fast tracking protocols and may be at elevated risk of prolonged postoperative ventilation.

Although the progress in liver transplantation owing to improved techniques in medicine is excellent, maintaining the stability of the patient who has marginal liver functions is critically complicated.

### **3.4 Hemodynamic and haematological management: The three phases of liver transplantation**

#### **3.4.1 The preanhepatic phase**

The **preanhepatic phase** involves dissection and mobilization of the liver. Hemodynamic instability may be seen as a result of drainage of liters of ascitic fluid, transection of large varices and surgical manipulation of the liver, temporarily obstructing venous return. However, in this period of liver transplantation, the primary issue is surgical bleeding. Several approaches have been applied to reduce bleeding: preoperative autologous blood donation, erythropoietin administration, intraoperative isovolemic hemodilution, blood salvage, maintenance of low intraoperative central venous pressure (CVP), and normothermia to prevent hypothermia-induced coagulation abnormalities (Chibber et al, 2007). The low CVP approach maintaining the pressure at or below 5 cm H<sub>2</sub>O has been shown to provide an 80% reduction in blood loss, although the usage of this strategy still remains controversial (Liu & Niemann 2011). Fluid resuscitation results in a decrease in coagulation factors and platelet count (Murray et al, 1995). Packed red cells and fresh frozen plasma should be prepared at this time. During this time period for the evaluation of the coagulation, thromboelastograph and standard laboratory tests (prothrombin time, fibrinogen and platelet count) can be used. Monitoring coagulation parameters differs, but the prothrombin time, INR, partial thromboplastin time, fibrinogen and platelet counts are monitored in most of the transplantation centers. While thromboelastography is used in approximately 33% of centers, the activated clotting time is used in approximately 18% of centers (Schumann et al, 2003). Excessive treatment of coagulopathy is not usually recommended at this phase unless bleeding is extreme. As a result of improved intraoperative techniques, some centers reported average RBC transfusion rates as low as 2 U (De Boer et al, 2005). The requirements for the blood products has been reduced for over the last decade, that several reports revealed the number of liver transplants without any administration of blood products has been increased. Because, blood transfusion may have its own adverse events such as; subacute transfusion complications including fluid overload, hypothermia, hypocalemia, hyperkalemia, acid-base disturbances; and more seriously, acute hemolytic transfusion reactions, infusion of a bacterially contaminated unit, transfusion associated lung injury, severe allergic reactions and anaphylaxis; moreover immune modulation associated with worse outcome (Niemann, 2010; Hannaman & Hevesi, 2011). Diuretics can be used to maintain euvolemic conditions and reduce transfusion requirements. Mannitol, with its potential for free radical scavenging and antioxidant properties, can help to remove free water in the abdominal organs, which is due to the congestion of blood flow through the fibrosed liver; particularly being useful in hepatorenal syndrome. Mannitol can be used before clamping or during the anhepatic phase (Vater et al, 2004) (Table 3).

Calcium chloride administration during the absence of hepatic functions avoids citrate intoxication related with the infusion of citrate rich blood products (Scott et al, 1996).

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 hemodynamic instability.

#### **3.4.2 The anhepatic phase**

The **anhepatic phase** starts with the occlusion of blood inflow to the liver and ends with graft reperfusion. The procedure of clamping the inferior vena cava and portal vein, and

dividing the hepatic vasculature (including IVC) results in the loss of venous return leading to a high risk of 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 promotes edema and ischemia of intestines. This may be overcome by veno-venous bypass which involves cannulation of portal and femoral veins, diverting the blood flow from IVC and portal veins to the axillary vein; improving renal perfusion pressure, lessening splanchnic congestion and delaying the development of metabolic acidosis (Findlay, 2002; Steadman, 2004). VVB improves hemodynamic stability, reduces blood loss, and allows extra time during the anhepatic phase. The first successful use of venovenous bypass (VVB) is reported in 1984 (Shaw et al, 1984). Venovenous bypass is used only in some centers. Although there are many benefits of venovenous bypass such as reducing hemodynamic instability and blood loss during anhepatic phase, maintaining intraoperative renal function and cerebral perfusion pressure in patients with acute fulminant failure by avoiding rapid swings in blood pressure (Shaw et al, 1984; Chari et al, 1998; Grande et al, 1996; Veroli et al, 1992), the use of it is not without risk such as; air embolism, thromboembolism, brachial plexus injuries and incorrect cannulation which may be mortal and may increase the risk of morbidity. The decision of using VVB depends on medical team experiences, preferences and judgement. The volume restriction brings the usage of vasopressors, as an alternative to veno-venous bypass. Transient inotropic support in addition to blood and fluid replacement is often required until effective veno-venous bypass is established. Norepinephrine and vasopressin improve circulatory stability and renal perfusion without impairing the mesenteric blood flow (Wadei et al, 2006; Alessandra et al, 2007). In order to preserve renal functions, prophylactic mannitol administration prior to and during venous clamping may be beneficial.

Transfusion of blood leads to a large citrate load that can no longer be metabolised when the liver is removed, resulting in hypocalcemia and secondary myocardial depression. Treatment with periodic calcium chloride administration should be guided by ionized calcium concentration measurements to avoid hypercalcemia. On the other hand, acid metabolites originating from intestine and lower body cannot be cleared in the absence of liver, resulting in progressive acidosis. Sodium bicarbonate therapy should be guided by arterial blood gas analysis, because excessive administration may result in hypernatremia, hyperosmolality and metabolic alkalosis. Although hypoglycemia can occur, hyperglycemia is more likely, due to the large amounts of transfused blood products. Glucose containing solutions are not used unless hypoglycemia is documented. Due to absence of a liver produced plasminogen activator inhibitor, fibrinolysis may begin during this phase. During this significantly notable phase platelets and coagulation factors continue to decrease. Antifibrinolytic strategies differs among centers. Postreperfusion syndrome may follow within a few minutes with severe hypotension, decreased heart rate, and a major decrease in systemic vascular resistance together with an increase in pulmonary artery pressure (Table 3).

After hepatectomy, vascular anastomoses of the supra- and infra-hepatic inferior vena cava and the portal vein are performed.

### 3.4.3 The neohepatic phase

In **neohepatic phase**, when the venous anastomosis to the graft is completed, the liver is flushed with blood and the clamp on IVC is released. 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. Aggarwal described 'postreperfusion syndrome' (PRS) in 1987, and defined it as at least 30% decrease in mean systemic blood pressure for more than 1 min during the first 5 min following reperfusion and by initial reperfusion of the hepatic artery (Aggarwal et al, 1987; Moreno et al, 2006). Despite the restoration of blood volume, electrolyte and acid base balance, hypotension and bradycardia are also common. Avoiding excessive fluid administration and hypervolemia is one of the intraoperative aims, maintaining a low CVP via IV volume restriction or phlebotomy (Massicotte et al, 2006). Besides volume restriction, plebotomy or using both; nitroglycerin may become a pharmacological alternative, in patients whose blood pressures are tolerable, to keep the CVP low (Massicotte et al, 2006; Hannaman & Hevesi, 2011).

Significant hemodynamic changes such as decreased cardiac output, increased splanchnic and lower caval pressures, decreased renal perfusion pressure, and reduced systemic arterial pressure may be seen during this period. Mediators may be released by the ischemic liver including xanthine oxidase, a generator of cytotoxic oxygen radicals which may produce myocardial and cellular damage. Strong vasopressors with an alpha-agonist action such as norepinephrine may be required (Ramsay et al, 1992). These changes related to reperfusion may be decreased by using the piggy back technique contributing to a side-bite of IVC allowing the venous return to continue (Findlay, 2002; Gurusamy et al, 2011). Initial arterial reperfusion may be preferable only in patients with poor cardiac reserve (Moreno et al, 2006). Hypothermia is a marker for the presence of graft outflow into the central circulation. Calcium chloride should be given for treating life-threatening hyperkalemia and possibly bicarbonate administration must be considered. Electrocardiographic changes require prompt treatment. Even in the absence of treatment, increased potassium levels fall spontaneously within minutes due to redistribution. The severe coagulation disorder seen in this period is mainly multifactorial in its etiology including reperfusion hypothermia, ionized hypocalcemia, dilutional coagulopathy, quantitative and qualitative defects in platelets, heparin effect, fibrinolysis and humoral substances released by the grafted liver (Pvalizza et al, 2001; Hannaman & Hevesi, 2011). Infrequently, excessive activation of coagulation may occur during this phase (Gologorsky et al, 2001).

Coagulation disorders should be corrected during this phase of the surgery to obtain sufficient results. However, using blood products may result in hypervolemic state and a paradoxical increase in blood requirement. Fibrinolysis, shown by the thromboelastograph, should be reversed with aminocaproic acid and antifibrinolytics or cryoprecipitate may be required. Thromboelastograph helps assessing both cellular and humoral components of whole blood coagulation and fibrinolysis; and also the effects of antifibrinolytic therapy, cryoprecipitate, fresh frozen plasma, platelet and protamin as treatment strategies. However, there have been some case reports of thromboembolic complications in patients treated with antifibrinolytic agents (Manji et al, 1998; Sopher et al, 1997; O'Connor et al, 2000; Gologorsky et al; 2007; Ramsay et al, 2004; Ellenberger et al, 2006). A systematic review and meta-analysis of the safety of antifibrinolytic drugs has not shown any relationship with thrombosis in liver transplantation (Molenaar et al 2007). Certainly, antifibrinolytics should not be used prophylactically in patients with a history of thrombotic events.

Signs of liver function which may be seen in the operating room are decreased calcium requirements, improvement in acidosis, increased urine output, rising core temperature and

biliary output from the graft. As the graft begins functioning the coagulopathy gradually improves. Fibrinolysis and heparin effect ceases within 2 hours, coagulation factors and platelets begin to increase toward baseline levels; prothrombin time and activated partial thromboplastin time reach their baseline values within a few days (Hannaman&Hevesi, 2011) (Table 3).

|                    |  |
|--------------------|--|
| Preanhepatic phase | <ul style="list-style-type: none"> <li>• Baseline Tests</li> <li>• Intravenous antibiotics</li> <li>• Warmers</li> <li>• Incision</li> <li>• Induction of anesthesia</li> <li>• Invasive monitoring (arterial catheter, pulmonary catheter)</li> <li>• Lower CVP (5 cm H<sub>2</sub>O), restriction of iv fluid administration, phelobotomy if Hgb&gt;10 g/dl</li> <li>• Vasopressin (Norepinephrine) to keep mean blood pressure (BP)&gt;60 mmHg</li> <li>• Epinephrine or dopamine to preserve cardiac output (C.O)&gt;5L/min</li> <li>• Maintain Hgb &gt;7 g/dl, platelets&gt;40.000, MA (TEG)&gt;45mm, fibrinogen&gt;100 mg/dl</li> <li>• Prior to clamping, iv mannitol 0.5 g/kg</li> <li>• Just before clamping <ul style="list-style-type: none"> <li>• IV Heparin 3-5000 U</li> <li>• Increase CVP to 10 cm H<sub>2</sub>O</li> <li>• In severe hypoalbuminemia 25%</li> </ul> </li> </ul> |
| Anhepatic Phase    | <ul style="list-style-type: none"> <li>• Maintain Hgb &gt;7 g/dl</li> <li>• IV fluids to keep CVP around 5 cm H<sub>2</sub>O</li> <li>• Vasopressin/Norepinephrine to preserve BP&gt;60 mmHg and C.O&gt;5 L/min</li> <li>• Correct base deficit</li> <li>• Normocalcemia</li> </ul>  |
| Neohepatic Phase   | <ul style="list-style-type: none"> <li>• Reperfusion</li> <li>• IV vasopressin 1-5 U bolus to keep BP&gt;60 mmHg</li> <li>• Euvolemia (CVP 5-10 cm H<sub>2</sub>O)</li> <li>• Dopamine/epinephrine to preserve C.O&gt;5L/min</li> <li>• Norepinephrine/vasopressin to preserve BP&gt;60 mmHg</li> <li>• Transesophageal Echocardiography if necessary</li> <li>• Maintain Hgb&gt;7 g/dl, platelets&gt;40.000, fibrinogen&gt;100 mg/dl</li> <li>• TEG: <ul style="list-style-type: none"> <li>• Protamin 30 mg iv if R is more</li> <li>• Maintain MA&gt;45 mm with platelet infusion</li> <li>• If Ly30&gt;8% iv EACA 5gr</li> </ul> </li> <li>• Consider fast tracking</li> </ul>   |

Table 3. The evidence-based protocol for liver transplantation that is outlined by University of Wisconsin (Hannaman & Hevesi, 2011)

### 3.5 Sodium, potassium and glucose management in organ transplantation

A lot of recent studies have investigated electrolyte and glucose management in organ transplantation. In the last decade, anesthesiologists paid attention to intraoperative glucose management. Interaction between glycemic control and organ transplantation were recently reviewed (Marwin&Morton, 2009). Hyperglycemia increases the expression of adhesion molecules and the production of cytokines, increases ischemic damage and the inflammatory response to ischemia/reperfusion (Marwin & Morton, 2009). In addition to this; the documented risk of hypoglycemia with intensive insulin therapy has led to the modification of more conservative glycemic targets, but investigation of glycemic control in transplant recipients are limited. Although transplant patients were not specifically mentioned, The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) reported a consensus statement on glycemic control (Moghissi et al, 2009). A perioperative 'middle ground' target glucose of between 140 and 180 mg/dl seems appropriate (Keegan & Wright, 2010; Lazar et al, 2009). However, studies of glucose management in transplant recipients are limited.

In transplant patients, predictors and potential treatments especially for perioperative hyperkalemia has been documented, because hyperkalemia leading to ventricular fibrillation is still reported, although in most patients a progressive decrease is seen. A retrospective analysis of 1124 liver recipients showed that 10.2% of patients had hyperkalemia with high baseline potassium values (Xia et al, 2007). High recipient potassium concentrations were found to be an independent predictor of death within the first year after liver transplantation (Dawwas et al, 2009). Bank blood transfusion imposes a severe potassium increase, and hyperkalemia may complicate the status of the transplant patient, especially in the presence of renal impairment and acidemia (Nakasuij& Bookallil, 2000). Serum potassium concentrations must be checked periodically and prereperfusion hyperkalemia must be corrected aggressively. Treatments are administration of insulin-glucose and/or salbutamol, furosemide, washing of bank blood using cell-salvage equipment, and hemodiafiltration. The effectiveness of different volumes of 5% albumin solution for the washout of preservation fluid in liver transplant grafts prior to reperfusion was measured; proposing the minimal washout fluid volume as 500 ml to reduce the risk of postreperfusion syndrome and hyperkalemia (Homvise et al, 2008). During neohepatic period baseline hypokalemia, low body weight (pediatric patients), administration of fresh-frozen plasma units and absence of ascites at surgery were independent predictors for hypokalemia (Xia et al, 2006). Potassium should be administered carefully, since it leads to hyperkalemia easily and is more likely to be dangerous than no treatment.

Besides, hyponatremia occurs in approximately 20% of patients with decompensated cirrhosis and has been shown to be a predictor of death for patients with end-stage liver disease listed for liver transplantation (Kim et al, 2008). The brain adapts to hyponatremia by losing intracellular solutes limiting brain edema (Gines P & Guevara, 2008). Treating hyponatremia may prevent hepatic encephalopathy. While correcting hyponatremia rapidly in the presence of lack of adaptation by the brain may lead to osmotic demyelination syndrome. Central pontine myelinolysis (CPM) in liver transplant recipients appear to be associated with a rapid rise in serum sodium concentration in previously hyponatremic patients (Zhang et al, 2009). This syndrome is often associated with neurological morbidity and mortality. A review of 1247 patients undergoing liver transplantation reported 11

patients diagnosed with CPM by neurological imaging findings (Lee et al, 2009). Patients with hyponatremia can be successfully operated but they are at increased risk of cerebral demyelination syndromes. In one report rapid correction of hyponatremia causing a perioperative rise of 21-32 Meq/L in the serum sodium were associated with central pontine myelinolysis, while an increase of 16 mEq/L was not (Wszolek et al, 1989). The first step in management of hyponatremia is determination of the patient's volume status (Gines P & Guevara, 2008).

### 3.6 Early-extubation (fast-tracking)

In general, fast tracking of a patient refers to improvement in quality of care, short length of stays in ICU and hospital and reduced costs of total treatment. Prolonged mechanical ventilation is no longer desired, for a group of patients devoid of risk factors, following orthotopic liver transplantation (OLT). 'Fast-tracking' defined as tracheal extubation at the conclusion of surgery before leaving the operating room, varies widely among the centers for OLT recipients. In liver transplantation the aim is rapid progress from preoperative preparation throughout the surgery and early discharge from hospital. Because of the nature of this procedure; awaiting recipients for a cadaver liver donor graft, fast-tracking contributes to intra- and post-operative surgical and anesthesiological strategies; meaning generally a reduction in the postoperative ventilation time (Glanemann, 2007).

In recent years there is a gradual increase in the number of early extubated recipients approaching to approximately 70-80% (Forraz-Neto et al, 1999; Park et al, 2000; Biancofiore et al, 2005; Salizzoni et al, 2005). Postoperative positive airway pressure ventilation combined with sedation has been known to decrease surgical stress response, improve haemodynamic stability and facilitate early recovery; however leading to elevated intrathoracic pressures it causes an increase in pulmonary vascular resistance which in turn rises right ventricular afterload. The possible associated tricuspid regurgitation there may occur venous congestion in the graft (Jullien et al, 1995). On the other hand, spontaneous breathing has been shown to reduce intrapleural pressures, improving venous return and hepatic blood flow; leading to a better recovery (Kaisers et al, 1995). Fast-tracking combined with the restrictive fluid management have been shown to result in rapid recovery (Rossaint et al, 1990).

Fast-tracking of the patients with liver transplantation is usually safe and well tolerated; postoperative mechanical ventilation is no longer required for the majority of patients who are devoid of risk factors (Glanemann, 2007). However, as the Model for end-stage liver disease (MELD)-score based organ allocation system has been introduced, the number of patients to be the candidates for fast-tracking is decreased; because it has been shown that early extubation also has its own complications including postoperative ventilatory failure resulting in impaired oxygen delivery to the new graft and reintubation for early surgical complications such as bleeding, bile leak, thrombosis or retransplantation (Mandell et al, 2007).

**Risk factors** for prolonged mechanical ventilation after liver transplantation has been described in a statistical analysis. According to this analysis, encephalopathy and a body mass index  $>34$  were significantly associated with failure, thus cannot be extubated in the operating room. Primary graft dysfunction, renal failure, cardiovascular failure, neurological

impairment, use of >12 units of red blood cells and pulmonary edema cannot tolerate extubation within 3 hours postoperatively. Acute liver failure, retransplantation, severe preservation injury to the graft, mechanical ventilation prior to surgery and use of >15 units of red blood cells and fresh frozen plasma require mechanical ventilation at least 24 hours postoperatively (Mandell, 2002).

### 3.7 Pain management

Orthotopic liver transplant patients were reported to experience less pain and use less morphine in the postoperative period compared to liver resection patients (Moretti et al, 2002). Chen et al have found morphine consumption significantly lower in patients with end-stage liver disease undergoing living-donor liver transplantation; compared with healthy living liver donors and patients with liver cirrhosis due to chronic hepatitis B or C virus infection and hepatocellular carcinoma undergoing hepatectomy, only on the first postoperative day (Chen et al, 2010).

Epidural anesthesia and analgesia provide a good quality of pain relief after major surgery. Considering the well known coagulation disorders associated with liver surgery, epidural hematoma formation is a major risk. Nowadays, although it seems that epidural analgesia for living liver donor is a safe method for analgesia, it may be hazardous for recipients because of unpredictable coagulopathies after liver transplantation (Lukanovic et al, 2008).

The type of surgical incision, in particular upper midline compared with subcostal incision affects postoperative pain, but the safety and efficacy needs to be further evaluated (Kim et al, 2009).

### 3.8 Postoperative adverse events

#### 3.8.1 Early complications (Table 4)

**Hypothermia:** In the intensive care units it takes 3-8 hours to warm a patient; during this period of hypothermia and warming there is always a risk of arrhythmias. Also during this period, shivering causes the metabolic rate to increase.

**Prolonged mechanical ventilation:** Over 72 hours of mechanical ventilation is required for 15% of the patients; mainly due to preoperative malnutrition, postoperative hemorrhage and primary non-functioning donor graft.

**Bleeding:** The requirements for blood transfusion continues also in the postoperative period. In reoperations a bleeding site is often found, however in a majority of patients this can also be caused by coagulopathy. Prothrombin time may remain high in the postoperative period and also thrombocytopenia may develop because of the sequestration during recirculation. Thromboelastogram is a useful monitor also for the coagulopathy in the postoperative period.

**Hypertension:** The hyperdynamic circulatory state tends to become normal during the posttransplantation period, however in 55-85% of patients hypertension may develop, resulting in intracranial hemorrhage.

**Impaired liver function tests:** Within the first 48-72 hours, inadequate perfusion of the graft, venous congestion and edema may lead to functional impairment. However, in the following period coagulopathy improves, whereas aminotransferase, alkalene phosphatase and bilirubin levels start to decrease.

**Malnutrition:** The patients with end-stage liver disease are often malnourished and have depleted protein stores. Following transplantation protein catabolism occurs, leading to a negative nitrogen balance within a month. This protein catabolism results in an increase in urinary 3-methylhistidine levels, revealing this catabolism originates from muscle.

**The primary non-functioning of donor graft:** The increase in the levels of liver enzymes within 1 week after transplantation refers to acute cellular rejection, which requires biopsy for the definitive diagnosis. Retransplantation is necessary before the other organs are affected.

**Sepsis:** Most of the patients are transferred back to the ICU because of sepsis, following their discharge from ICU. Selective intestine decontamination may limit bacterial infections, however non-bacterial organisms contribute to a major problem.

**Others:** Bile leak, thrombosis of hepatic artery and portal vein may be major complications during this period. Moreover, hyperglycemia, renal insufficiency and neurologic impairments may also occur, as side-effects of immunosuppressive therapy.

### 3.8.2 Late complications (Table 4)

Obesity (30-40%), hyperlipidemia (30%), diabetes (13-30%), osteoporosis and malignancy may occur due to the long-term immunosuppressive therapy (Lopez et al, 2006).

|                            |  |
|----------------------------|--|
| <b>Early Complications</b> | <ul style="list-style-type: none"> <li>• Hypothermia</li> <li>• Prolonged mechanical ventilation</li> <li>• Bleeding</li> <li>• Hypertension</li> <li>• Impaired Liver Function Tests</li> <li>• Malnutrition</li> <li>• The primary non-functioning of donor graft</li> <li>• Sepsis</li> <li>• Others</li> </ul> |
| <b>Late Complications</b>  | <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Hyperlipidemia</li> <li>• Diabetes</li> <li>• Osteoporosis</li> <li>• Malignancy</li> </ul>  |

Table 4. Postoperative Adverse Events after liver transplantation

## 4. Anesthesia for non-transplant surgery in liver-transplanted patients

Liver transplant recipients may return to the operating room for reexploration, which is frequently for biliary reconstruction. In these cases, liver usually functions normally, leading

to anesthetic considerations including regional techniques such as epidural catheters similar to any abdominal procedure (Baker et al, 2005). The liver grafts that are functioning appropriately can metabolize the drugs effectively, however this functioning should be assessed. Coagulation abnormalities should be treated with vitamin K or FFP, ascites with diuretics or paracentesis and encephalopathy should be avoided with lactulose administration and careful use of sedatives; these may improve outcome in these patients. Renal functions should also be assessed, moreover hypertension may be a common problem in these patients. Stress dose of corticosteroids may be required for patients who receive chronic supplementation. Because of the powerful immunosuppressive therapy, steril conditions should be optimized for the placements of venous and epidural catheters. Drugs that may decrease hepatic blood flow should be avoided (Steadman, 2004).

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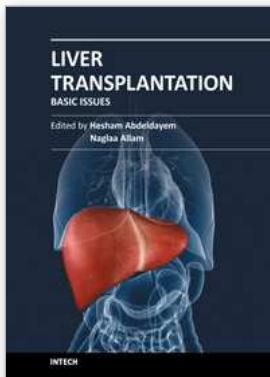
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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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### InTech Europe

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
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Phone: +86-21-62489820  
Fax: +86-21-62489821

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