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Anesthesia for liver transplantation☆

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A B S T R A C T

Patients with end stage liver disease (ESLD) have complex problems such as cirrhotic cardiomyopathy, coronary artery disease, hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH), hepatic encephalopathy, intracranial hypertension, (ICP), left ventricular outflow tract obstruction (LVOTO), high Model of end liver disease (MELD) scores, hyponatremia, and coagulopathies. The anesthesia management for liver transplantation can be very complex, dynamic and challenging. Anesthesia agents affect hepatic blood flow and anesthetic drug distribution, metabolism and elimination maybe altered in end stage liver disease. Other non-anesthetic agents such as nitric oxide, epoprosterenol, THAM, hypertonic saline, fibrinogen concentrates, fresh frozen plasma, platelets, packed red blood cells, recombinant plasminogen activator, calcium chloride, epinephrine etc. may play a vital role in the perioperative management of these patients. Intraoperative hemostasis and coagulation management can be very arduous as these patients may bleed or be at risk for thrombosis. Monitoring modalities such as Thromboelastography (TEG), Transcranial Doppler (TCD), Transesophageal Echocardiography (TEE), Bispectral Index (BIS) and Optic Nerve Sheath Diameter (ONSD) ultrasound play a significant role in various circumstances. Surgical techniques include complete or partial occlusion of the inferior vena cava (IVC) with or without use of venovenous bypass (VVBP) or portocaval shunts. Post reperfusion syndrome (PRS) is a crucial event in this procedure, where patients may experience arrhythmia and/or cardiac arrest. Anesthetic handling of this phase has been recapitulated in detail. Provision of anesthesia services to the living liver transplant donor and pain management has been outlined.

1. Preoperative assessment

A detailed and complete preoperative evaluation of the liver transplant recipient is essential (Table 1). The Anesthesiologist should discuss the risk and benefits of general anesthesia, including participation of residents with the patient and/or significant other. Pre-operative NPO guidelines, intubation, intravenous access and any other invasive monitors used at the institution should be discussed along with inherent risks. At our institution, we explicitly discuss arterial lines, central venous access, pulmonary artery catheterization, use of intraoperative transesophageal echocardiography (TEE), thromboelastography (TEG), cell saver and transfer to surgical intensive care unit (SICU). The patient should be informed that she/he will be presented to the Liver Transplant Selection Committee and will be listed on the United Network of Organ Sharing (UNOS) -UNet as a potential cadaveric liver transplant recipient by the Transplant Center upon approval. The Model of End Liver Disease (MELD) [1] score is calculated to indicate severity of liver disease and is used by the UNOS and Organ Procurement and Transplantation Network (OPTN) for organ allocation. Other MELD scores include MELD sodium [2] and MELD Lactate [3].

Cirrhotic patients with end stage liver disease (ESLD) usually suffer from cirrhotic cardiomyopathy. It comprises increased cardiac output and a compromised ventricular response to stress. The performance of the heart declines and there is concomitant diastolic and systolic dysfunction due to activation of cardiac renin angiotensin system and impairment of the B-adrenergic receptor [4]. Low systemic vascular resistance, bradycardia and diastolic dysfunction are also commonly seen in ESLD. There are several electrophysiologic abnormalities found in cirrhotic cardiomyopathy. These include QT-interval prolongation, mechanical and electrical dyssynchrony, and chronotropic incompetence [5]. Liver transplant can lead to reversal of cirrhotic cardiomyopathy [5].

Additionally, ESLD patients are also at risk for significant coronary artery disease (CAD). It has been found that at least 25% of these patients have one of their coronary arteries either moderately or severely stenosed.

Hemodynamically significant left ventricular outflow tract obstruction (LVOTO) maybe produced due to left ventricular hypertrophy and hyperdynamic systolic function in ESLD. One retrospective review of 106 transplant recipients found inducible LVOTO on pre-operative dobutamine stress echocardiography (DSE) in 40% of patients [6]. In this study, an outflow gradient equal to or greater than 36 mm Hg was significantly associated with intraoperative hypotension.

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Table 1
Anesthesia preoperative evaluation and risk assessment.

- Visit Information including referral source and advanced directives.
- History of present illness: Cause of ESLD, presence or absence of cirrhosis, portal HTN, ascites, esophageal varices, encephalopathy, coagulopathy and thrombocytopenia. It is essential to delineate complications such as portopulmonary hypertension, hepatopulmonary syndrome and hepatic hydrothorax.
- The patient is willing to accept blood and or blood products, if needed during the procedure.
- Status of Esophageal Varices.
- Past Surgical history, family anesthesia history, social behaviors, medications and allergies.
- Review Of Systems – Respiratory System: asthma, cough, COPD etc., Cardiovascular system: HTN, Angina, MI, Afib, syncopy etc., Renal: ARF, CRI, dialysis etc., Endocrine: DM, thyroid etc., Gastrointestinal System: GERD, reflux, Hepatitis etc., Neurological System: Stroke, TIA, seizures etc., Psychiatry: depression, encephalopathy etc., Hematological system: bruising, bleeding tendency etc., Musculoskeletal: degenerative arthritis, osteoporosis etc., Dermatological: Rash, bruises etc.
- Physical Examination: Tracheostomy/intubated, Vital Signs, Airway Exam: Mallampatti Classification, Mouth Opening, Neck Mobility, Dentition, and Anticipated Difficult Intubation. Respiratory: AE, Cardiac: S1 S2, murmurs etc.; Psych: Alertness, orientation, memory etc.: Neurological: muscle weakness, paralysis, sensory deficit, neuropathy etc.: Skin: Rash, bruising etc.
- Results Review: Procedures/Diagnostic Studies such as EKG, 2 D Echo, Stress Test, Cardiac Catheterization, CXR/CT Chest/PFT
- ASA Physical Status. (ASA Physical Status 1 – A normal healthy patient, ASA Physical Status 2 – A patient with mild systemic disease, ASA Physical Status 3 – A patient with severe systemic disease, ASA Physical Status 4 – A patient with severe systemic disease that is a constant threat to life, ASA Physical Status 5 – A moribund patient who is not expected to survive without the operation. ASA Physical Status 6 – A declared brain-dead patient whose organs are being removed for donor purposes. E is added to denote Emergency Surgery.)
- MELD Score = (0.957 × Log e (creatinine mg/dl) + 0.378 × Log e (bilirubin mg/dl) + 1.12 × log e (INR) + 0.643) × 10, where S. Creatinine, Bilirubin and INR are prognostic factors, 0.957, 0.378 etc. are regression coefficients. (S. Creat >4 = 4, Any value < 1 = 1, Pts. on dialysis or prior 24 h. CVVHD = S. Creat of 4.).

MELD exception points or additional points are given to patients with:
Hepatocellular cancer (HCC) with Tumor 2–5 cm, <3 lesions –MELD equivalent of 15% probability of candidate death within 3 months. Alpha feto-protein >200 ng/ml., after ruling out metastasis, macrovascular involvement i.e. Portal/hepatic veins and non resectability, Hepatopulmonary syndrome (HPS), Portal HTN + shunt + PaO2 <60 mmHg on RA, Cholangiocarcinoma 3 cm or less, carbohydrate antigen, biopsy, cytology proven, exclude pts. with mets, Cystic Fibrosis with FEV1 <40%, Familial Amyloid Polyneuropathy with EF >40%, TTR gene mutation, biopsy proven amyloid involvement, Portopulmonary Syndrome with MPAP <35 mmHg, PVR <400 dynes s^{-1} cm^{-5}, TPG to correct volume overload and Primary Hyperoxaluria with AGT deficiency, combined kidney-liver listing, GFR <25 ml/min for 6 wks.

Preoperative echocardiography is essential to assess ventricular function and size, valvular function, and pulmonary artery pressure, and to exclude the presence of pericardial effusion or a significant LVOTO. Pre-operative echocardiography is also useful to calculate pulmonary artery systolic pressure. Screening for portopulmonary hypertension (POPH) is done assessing pulmonary artery systolic pressures (PASP) for values greater than 45–50 mmHg and/or right ventricular dysfunction. If the screen is positive, then right heart catheterization is performed. This is done to calculate the mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and transpulmonary gradient (TPG) [7].

Portopulmonary hypertension (POPH) can be described as pulmonary hypertension syndrome with vascular obstruction. There is increased resistance to pulmonary arterial flow due to varying degrees of pulmonary endothelial and smooth muscle proliferation, with added vasoconstriction and in-situ thrombosis [7] . Interestingly, development of POPH has no correlation with the severity of liver disease. The diagnostic criteria for POPH include a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest, a pulmonary vascular resistance (PVR) of greater than 240 dynes s^{-1} cm^{-5} and a PaOP <15 mm Hg in the presence of known portal hypertension [8]. POPH can be better assessed with the transpulmonary gradient (mPAP-PAOP). The transpulmonary gradient >12 mmHg reflects the obstruction to flow (PVR) and indicates the contribution of intravascular volume and high cardiac output to the mPAP [7,9].

5% to 10% of ESLD candidates have POPH of which 5% of ESLD candidates have moderate to severe POPH, with mean pulmonary arterial pressure (mPAP) 35 mm Hg. A pre-operative mPAP of 35–50 mm Hg has been associated with a 50% risk of mortality after LT in patients with POPH [10]. Mortality was almost 100% among patients with POPH and mPAP >50 mm Hg [7,11]. Therefore, POPH should be treated with vasodilators such as epoprosterenol, sildenafil, nitric oxide etc. As a MPAP >35 mmHg is seen as a contraindication to liver transplant, a consult to, and management by, a pulmonologist specializing in POPH therapy can reduce the MPAP to acceptable levels. In centers where PAC is not routinely used in these cases, it is indicated.

Hepatopulmonary syndrome (HPS) is characterized by arterial hypoxemia caused by intrapulmonary vascular dilatations. The clinical triad of 1) portal hypertension; 2) hypoxemia; and 3) pulmonary vascular dilatations characterizes the clinical picture of HPS [12]. Diagnostic Criteria for HPS as per European Respiratory Society/European Association for Study of the Liver Task Force includes liver disease, an A-a oxygen gradient >15 mmHg, pulmonary vascular dilatation documented by "positive" delayed, contrast-enhanced echocardiography with left heart, detection of microbubbles >4 cardiac cycles after right heart opacification of microbubbles and brain uptake >6% following 99mTc macroaggregated albumin lung perfusion scanning [7].

The most recent ACC/AHA guidelines in 2012, consistent with previous guidelines, stated that noninvasive stress testing should be used in liver transplant candidates if the patient has 3 or more risk factors for CAD and cited the test as effective for the prediction of mortality [13]. DSE has a negative predictive value of 85% [11], sensitivity of 85% and specificity of 87% for detection of CAD [14]. Nuclear single-photon emission computed tomography (SPECT) stress imaging has a limited predictive value due to the chronic vasodilatory state exhibited by patients with ESLD [15], and its specificity for detecting obstructive CAD by coronary angiography is only 61% [16]. Coronary angiography is the gold standard for detecting CAD, and should be performed before it becomes contraindicated due to an excessive bleeding risk caused by coagulopathy and/or thrombocytopenia.

Hepatorenal syndrome is a form of prerenal acute kidney injury that occurs in decompensated cirrhosis. Hepatorenal syndrome can be diagnosed when there is cirrhosis with ascites with a serum creatinine >1.5 mg/dL in the absence of parenchymal kidney disease, shock or treatment with nephrotoxic drugs. Additionally, there is no improvement of serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin [7,17]. Hepatorenal syndrome is a form of pre-renal acute kidney injury that occurs in decompensated cirrhosis. The syndrome is classified into two types: Type 1 is characterized by a doubling of the serum creatinine level to greater than 2.5 mg/dl in less than 2 weeks while Type 2 is characterized by a stable or slower progressive course of renal failure [18].

Hepatic encephalopathy occurs when circulating neurotoxins such as ammonia, GABA; and gut derived false neurotransmitters accumulate. There is altered neurotransmission by glutamate or altered cerebral energy homeostasis [7]. It is manifested clinically by neuropsychiatric abnormalities. In chronic liver failure, ammonia levels do not correlate with degree of encephalopathy, but are used to assess effectiveness of therapy. It is treated with lactulose or polyethylene glycol 3350-electrolyte solution [19].

2. Anesthesia agents and the liver

Anesthesia agents commonly used in liver transplantation (LTx) can be categorized into sedatives, induction agents, inhalational agents or volatile agents, muscle relaxants, opioids and reversal agents.

Anesthetic drug distribution, metabolism and elimination may be altered in end stage liver disease. The uptake and onset of anesthetic drug

action is usually unaffected as the liver is not involved. The hepatic clearance of an agent is dependent upon several factors such as volume of distribution, functional hepatic blood flow, hepatic extraction ratio and hepatic microsomal activity.

All anesthetic agents and techniques can reduce hepatic blood flow and hepatic oxygen uptake. Intraoperatively, mechanical ventilation, hypercarbia, positive end expiratory pressure, hypotension, hemorrhage, hypoxemia and surgery can decrease hepatic blood flow. If the decrease in hepatic blood flow is significant, it can result in parenchymal centrilobular necrosis [7].

Etomidate, ketamine and propofol are induction agents. Etomidate decreases hepatic blood flow [20] by either increasing hepatic arterial vascular resistance or decreasing cardiac output and blood pressure. In cirrhosis, though the clearance is unchanged, the actual clinical recovery time maybe unpredictable due to increased volumes of distribution. Ketamine has little impact on hepatic blood flow. Propofol has a vasodilator effect, ultimately increasing total hepatic blood flow [21]. The elimination kinetic profile of propofol does not change in cirrhosis, but the postanesthetic recovery times maybe longer [22].

Midazolam has a longer half-life, a reduced clearance, reduced protein binding, a longer duration of action and an enhanced sedative effect. Dexmedetomidine, an alpha-2 adrenergic agonist, with sedative and analgesic properties, is primarily metabolized in the liver. Dose adjustments are therefore indicated when used in patients with significant hepatic dysfunction. It has been found to attenuate liver and intestinal injury in patients undergoing elective hepatectomy [23].

All volatile anesthetics decrease the mean arterial pressure and portal blood flow. Desflurane and sevoflurane have very little or no effect on total hepatic blood flow. In general, during liver transplantation, patients with a high MELD score need less inhalational anesthestics than those patients with lower MELD scores during the prehepatic and anhepatic phases [24].

The metabolism of morphine is significantly reduced in advanced cirrhosis and may accumulate. The elimination half-life of morphine is prolonged. The sedative and respiratory depressant effects are exaggerated. Fentanyl is highly lipid soluble and is metabolized by the liver [7]. It has a short duration of action. Its elimination is not appreciably altered in patients with cirrhosis [25]. However, unlike fentanyl, plasma clearance and elimination of alfentanil is increased in patients with cirrhosis [26]. Remifentanil is a short acting synthetic opioid that is hydrolyzed by blood and tissue esterases. Its pharmacokinetics is unaltered in patients with severe liver disease [27].

Vecuronium and rocuronium are steroidal muscle relaxants. The liver metabolizes them. In cirrhotic patients, they have decreased clearance, prolonged half-lives, and prolonged neuromuscular blockade. Vecuronium infusion dose requirements were least in the neohepatic phase as compared to the anhepatic and prehepatic phases for living donor liver transplantation [28]. Continuous infusions of rocuronium in patients undergoing liver surgery can be rapidly achieved with sugammadex [29]. Atracurium and Cisatracurium undergo Hofmann elimination and ester hydrolysis respectively. Cisatracurium infusions during liver transplantation require increased dosages and result in prolonged recovery [30].

3. Blood and coagulation management

Bleeding during liver surgery could be either surgical or coagulopathic, or both. The preoperative international normalization ratio (INR) has no predictive value in relation to intraoperative blood loss [31–33]. ELSD patients lack protein c and S and profibrinolytics [33]. Cirrhotic patients with primary biliary cirrhosis or primary sclerosing cholangitis are at higher risk for developing thrombosis [33]. The value of fresh frozen plasma (FFP) administration to correct abnormal INR values is debatable. FFP administration may cause volume overload [31].

In Acute Liver Failure (ALF), coagulopathy is more severe. Factors V and VII have very short half lives, (12 and 4–6 h respectively) hence their concentrations fall first. This is followed by decrease in plasma concentrations of factors II, VII and X. A review was conducted by the US Acute Liver Failure Study Group in about 1000 patients with ALF. The mean INR in ALF was 3.8 +/− 4.0 (range 1.5–>10). Most had a moderately prolonged INR (1.5–5) and only 19% had an INR >5. Thrombocytopenia is common in ALF. 40% of patients had a platelet count <90,000 on admission [7,34].

As per the American Society of Anesthesiologists Practice Guidelines [35] in 2006, transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute. However, it is important to understand that these guidelines may not accurately relate to an acutely bleeding patient.

Rapid sequence induction is recommended in patients with tense ascitis to decrease the risk of aspiration. If there is tense ascites, surgical incision/paracentesis may result in hemodynamic instability. Intravenous colloid solutions such as albumin can be given administered concomitantly to prevent circulatory collapse. Intravascular volume re-equilibrium occurs 6–8 h after removal of larger volume of ascitic fluid [36]. Large volumes of colloids and crystalloids maybe given within a few minutes using rapid infusion devices which are commercially available. Red cell salvage can be facilitated with use of cell savers – with/without leukocyte filters. Blood administration may be associated with hypocalcemia due to citrate intoxication and hyperkalemia [7].

When appropriate, preoperative autologous blood donation and acute normovolemic hemodilution may be beneficial [31]. For expansion of intravascular volume, 5% albumin is a preferred colloid in liver surgery. Plasma protein fractions containing albumin and α and β globulins are available.

Blood products commonly used in liver transplant surgery include packed RBCs (PRBC), FFP, platelets and cryoprecipitate. PRBCs may be diluted using 5% dextrose in 0.4% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4. It is essential that at least 70% of transfused RBCs remain in circulation for at least 24 h after transfusion. The hematocrit of PRBCs is approximately 60%. The pH of stored blood also reduces to approximately 7.0 as the storage media is very acidotic. Storage induces biochemical lesions which impair enzymatic activity, negatively affect RBC morphology and promote rapid clearance after administration [37].

Citrate binds calcium and may produce hypocalcemia. Hepatic blood flow is reduced during surgery and anesthesia especially during the anhepatic phase of LTx, which further reduces citrate metabolism. In LTx, several amounts of calcium may need to be given perioperatively, to prevent citrate intoxication. Calcium chloride has a molecular weight of 147 whereas calcium gluconate has a molecular weight of 448. Therefore 10% calcium chloride provides three times more calcium than an equal volume of 10% calcium gluconate. Usually approximately 250 mg of calcium is supplemented for each unit of blood administered. However, replacement is best guided by laboratory values

Whenever blood is stored for more than 24 h, very few platelets exist. If multiple units are given to the patient, dilutional thrombocytopenia may occur. One platelet concentrate usually produces an increase of about 7000–10,000 platelets/mm^3 at 1 hour after transfusion to the 70-kg adult. Platelets are stored at room temperature. Fever, sepsis, and active bleeding etc. may lead to decreased survivals and decreased recovery of transfused platelets. Apheresis platelets are collected from one donor to avoid pooling of platelets from multiple donors. Platelets are also available as leukocyte-depleted and ultraviolet C or gamma irradiated [38].

FFP contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. More recently, the ASA Task Force [35] recommended the administration of FFP with the following guidelines: for correction of microvascular bleeding in the presence of increased (>1.5 times normal) prothrombin time (PT)

or partial thromboplastin time (PTT), for correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than 1 blood volume and when PT and PTT cannot be obtained in a timely fashion. Since INR is less sensitive and specific in ESLD patients, correction of deranged INRs with FFP should rely on the clinical scenario rather than laboratory values.

Additionally, fibrinogen levels in packed RBCs also decrease with increasing storage time, resulting in dilutional hypofibrinogenemia. This is common in liver surgery, and can be managed by use of cryoprecipitate. Cryoprecipitate contains von Willebrand factor and fibronectin. Cryoprecipitate contains factor VIII:C, von Willebrand factor, fibrinogen, factor XIII, and fibronectin [39]. All other plasma proteins are present in only trace amounts in cryoprecipitate. Cryoprecipitate is preferred over fibrinogen preparations as they carry a higher risk of hepatitis. It should be administered through a filter and be given within 6 h of thawing.

Intraoperative hemostasis panels consisting of INR, fibrinogen and platelet count maybe useful to guide transfusion therapy. However, there are no specific defined target laboratory values for ESLD patients undergoing liver transplantation as their coagulation profile is deranged and is different than any other set of patients and therapy should only be instated if clinically relevant.

Thromboelastography or TEG is a very useful intraoperative test for coagulation. It assesses the clots tensile strength and its rate of formation and stability (Fig. 1). R = Reaction time is the time of latency from the time that the blood was placed in the TEG® analyzer until the initial fibrin is formed [7]. Preferred therapy for abnormal values is FFP. A = The value measures how fast the fibrin builds up and crosslinks – indicates the speed of clot strengthening. Preferred therapy for abnormal A is Cryoprecipitate. K = time measures how fast the clot reaches certain strength. Preferred therapy for abnormal values is FFP. MA = Maximum Amplitude represents maximum dynamic properties of fibrin and platelet bonding, reflecting the ultimate strength of the fibrin clot. Abnormal MA is treated with platelets. Thus goal directed therapy is facilitated. Fibrinolysis can be diagnosed using the TEG. If it is clinically significant, then it can be treated with small doses of Epsilon Aminocaproic acid or Tranexamic acid. Factor VII has been used to control massive bleeding during liver transplantation, but its true efficacy has not been proved [40]. Newer modalities of TEG are rapid thrombelastography (r-TEG) and functional fibrinogen thrombelastography (FF-TEG), and FIBTEM [41]. r-TEG correlates with k-TEG strongly for MA and FF-TEG estimates the plasma fibrinogen level well at the baseline [42]. Fibrinogen concentrates can be used for clinically relevant fibrinogen therapy. The dosage can be titrated with clot firmness as determined by the FIBTEM [41]. Alternatively, when diffuse bleeding is detected, a plasma fibrinogen value <1 g/L should be the aim [43].

4. Neurologic and hemodynamic management

Raised intracranial pressures (ICP) is common in patients with ALF. Reperfusion in a new liver graft may increase cerebral blood flow (CBF), subsequently increasing intracranial pressure (ICP) in liver transplant recipients. Severe post-transplant brain injury occurred at a rate of 7.8% and was associated with severe pre-transplant cerebral edema and a higher post-transplant INR [44].

In current clinical practice the ICP is measured invasively using an intracranial (ventricular, parenchymal, subdural, or extradural) catheter connected to or integrated with a pressure transducer. However, liver transplant recipients with coagulopathy are at risk of intracranial hemorrhage caused by invasive monitoring techniques. When an intracranial pressure monitor was used in acetaminophen acute liver failure, there was no significant 21-day mortality benefit. In nonacetaminophen acute liver failure, it may be associated with worse outcomes [45]. Therefore, most neurosurgeons are hesitant to perform this procedure without correction of the international normalized ratio (INR) to approximately 1.6 [46].

Both plasma and recombinant activated factor VII (rFVIIa)-based algorithms can be used to correct coagulopathy in preliver transplant patients with acute liver failure requiring ICP monitor placement [47].

The second most popular brain monitoring modality is brain tissue oxygenation (PbtO2). A thin electrode, able to detect oxygen content, is introduced into the brain parenchyma, allowing only a very small sampling area. The main problem in PbtO2 is that it may change dramatically, with changes in regional blood flow in different regions of the brain [48].

Transcranial Doppler (TCD) has also been used intraoperatively in liver transplantation. Autoregulation maybe impaired even in absence of acute fulminant liver faiure [49]. The diagnostic sensitivity of TCD for intracranial hypertension is 67% [50].

Recently, Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) was introduced recently as a useful noninvasive method for evaluating ICPb [51]. An optic nerve sheath diameter >5 mm by ocular ultrasonography is useful for evaluating ICP >20 mmHg noninvasively and has been used in perioperative LTx [51]. However, it has been found that the measurement of ICP by two-depth TCD is more reliable than the ONSD for detecting ICP >14.7 mmHg [52].

Measures used to reduce ICP during LTx include hyperventilation, use of hypertonic saline, mannitol and propofol. Hyperventilation lowers PaCO2 causing cerebral vasoconstriction decreasing ICP, may restore cerebral autoregulation and minimizes hyperemic cerebral edema [53]. Hypertonic saline (HTS) given as either a bolus or continuous infusion concentrated saline increases serum tonicity and further reduces cerebral swelling to reduce episodes of elevated ICP [54]. Mannitol may adversely affect mortality when compared to hypertonic saline [55]. Recently, HTS has been cited as superior to mannitol due to its excellent tonic properties and lack of hypovolemic hypertension [54]. With an intact blood brain barrier (BBB), very little sodium can cross it since its reflection coefficient is 1. Thus sodium pulls fluid out of the interstitial space.

When HTS is used, it is important to monitor serum sodium levels. A study denoted that approximately 28% of patients on the OLT waiting list have mild hyponatremia (125–134 mmol/L) and 3% have severe (Na <125 mmol/L) hyponatremia [56]. A relatively rapid increase in serum sodium in hyponatremic individuals, more than 12–15 mmol/L during surgery [57,58] has been associated with central pontine myelinolysis.

Propofol is an anesthetic induction agent. Frontal spindles are replaced by polymorphic 1–3-Hz activity as consciousness is lost. When the dose is increased further, periods of suppression are lengthened. They are interspersed with periods of activity. With a very high dose, EEG silence results [59]. EEG-derived indexes such the Bispectral Index (BIS), E-Entropy, Narcotrend, Cerebral State Index, the Patient State Index and NeuroSENSE are based on different algorithms. The most widely used monitor is the Bispectral Index. It uses a sensor on the patient's forehead to measure electrical activity in the brain. It then uses algorithms to process the EEG data and calculate a number between 0 and 100. 0 is the absence of brain electrical activity and 100 denotes that the patient is wide awake. A target range of BIS values during GA is 40–60 [60], whereas BIS between 0 and 5 denotes almost absent activity. When the brain activity is absent, oxygen consumption is markedly reduced. Thus when the ICP is very high resulting in compromise of cerebral tissue oxygenation, propofol may be used to reduce oxygen consumption. Propofol in doses of 30–50 $\mu g\ kg^{-1}\ min^{-1}$ effectively reduces ICP for a prolonged period [61]. Liver failure does not influence propofol pharmacokinetics.

The surgical technique used has a significant impact on intraoperative hemodynamics. The partial clamp inserted in the piggyback method allows some venous return, thereby preventing an acute reduction in the preload during IVC cross clamping (CC). When the patient is unable to tolerate the test cross clamp, it may be prudent to consider venovenous bypass(VVBP). Currently, in the US, venovenous bypass is routine in 51% of academic transplant centers. Partial venous occlusion

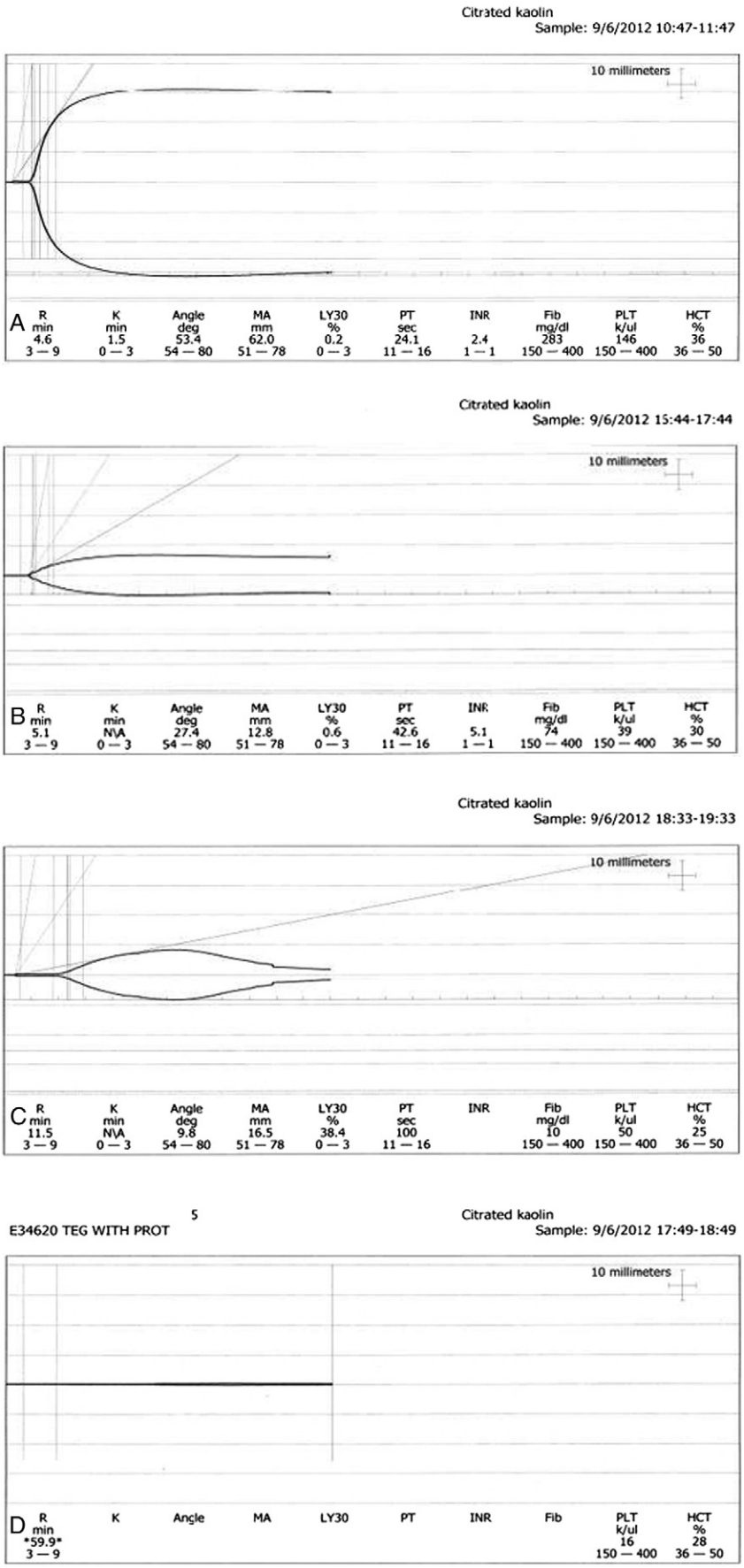

Fig. 1. (A) Normal TEG. (B). TEG showing decreased angle and maximum amplitude. (C) TEG showing fibrinolysis. (D) Flat line TEG.

was practiced in 76% of programs while total venous occlusion was used in 47% of centers. Low central venous pressure (CVP) technique was practiced in 54% of centers [62]. Vasopressin infusions, at low doses of 3.8 +/− 1.1 U/h have been used in certain institutions to decrease portal vein pressures and flow prior to the anhepatic phase, without decreasing cardiac output or intestinal perfusion [63].

Invasive hemodynamic monitors may include an arterial catheter, central venous catheters, a 9 Fr. catheter and an 18 Fr veno-venous bypass [VVB] return cannula in an internal jugular vein), or a 9 Fr. multiple access lumen catheter (MAC) and a rapid infusion catheter (RIC), a pulmonary artery catheter, and a transesophageal echocardiography (TEE) probe. Most academic centers routinely use pulmonary artery catheters. Reports of the risk of PAC use such as ventricular arrhythmia during LTx have been reported [64,65]. The role of newer non PAC derived parameters which measure pulse pressure and stroke volume variation, as well as extravascular lung water, remains to be determined. Nitric oxide and epoprosterenol infusions have been used to lower raised pulmonary artery pressures. Inhaled nitric oxide activates guanylate cyclase to from cGMP that medicates smooth muscle relaxation. Doses ranging from 10-40 ppm are effective to reduce pulmonary hypertension during liver transplantation. Epoprosterenol is a synthetic prostacyclin PGI2 that can be used intraoperatively in doses from 2–12 mcg/kg min^{-1}. It is delivered by a special pump since its half-life is very short, approximately 3–5 min [66]. It elicits a greater pulmonary vasodilator vasodilatory response than inhaled nitric oxide by decreasing both PAP as well as PVR [67]. Patients with pulmonary hypertension who achieve recovery to World Health Organization's functional class I or II with endothelin receptor antagonists have same survival as those treated with intravenous epoprosterenol [68]. Treprostinil, a newer prostacyclin analogue, is a pulmonary vasodilator with several routes of administration [69]. It has been used to successfully manage moderate to severe portopulmonary hypertension.

The patient should optimally metabolized before reperfusion. Blood sampling is done 3-5 minutes before reperfusion, to normalize the hematocrit, acid-base status, ionized calcium and potassium concentrations. Hyperkalemia is a common cause of reperfusion arrhythmia and arrest. Thus it may be prudent to lower potassium levels and optimize ionized calcium levels. Post reperfusion syndrome (PRS) is defined as a decrease in the mean arterial pressure of more than 30% of the value observed in the anhepatic stage, for more than 1 minute during the first 5 minutes after reperfusion of the graft [7]. When the graft is reperfused, and the portal vein, hepatic vein and IVC are unclamped, there is release of liver preservative solution as well as unknown vasoactive substances from the liver graft into the circulation. This results in sudden hyperkalemia, acidosis and hypothermia. Although volume status should be optimized, epinephrine is commonly used to treat PRS by supporting cardiac function and maintaining an adequate perfusion pressures [70]. Norepinephrine, dopamine and phenylephrine are commonly used vasopressors for management of PRS. Severe metabolic acidosis is treated with tromethamine (THAM). Sodium bicarbonate can be used to create a transient shift in the H+/K+ pump for hyperkalemia treatment. Severe Ischemia reperfusion injury is associated with lower PVF, HAF and TLBF [71]. Post reperfusion vasoplegia may occur which is refractory to pressors such a norepinephrine and epinephrine. A few case studies report management of this vasoplegia with an IV infusion of methylene blue (0.5 mg kg^{-1}) after a bolus dose [72]. Methylene blue can compete with NO in binding to the iron heme moiety of soluble guanylate cyclase. This inhibits the production of cGMP and preventing relaxation of the vascular smooth muscle [73]. Vasoplegia has also been reported due to anaphylaxis to a component of the University of Wisconsin (UW) preservation solution [74]. Elements of UW solution – allopurinol, hydroxyethyl starch and adenosine have been previously reported as anaphylactic triggers. But the hemodynamic stability during PRS has been greater when UW solution was used as compared to Histidine-Tryptophan-Ketoglutarate (HTK) Solution [75].

TEE is a becoming a more prevalent diagnostic and monitoring modality for LTx in the United States. In 2008, a survey from 30% of high volume LT centers reported 86% of anesthesiologists performed TEE in some or all LT cases. Only 12% of users were board certified to perform TEE [76]. However, in a survey published in 2014, 38.0% of centers in the US routinely used TEE in liver transplantation. 57.0% used TEE only in special cases or rescue situations. Thus the overall rate of use was 94.9%. 69.9% of transplant anesthesiologists were supposedly proficient in echocardiography. A major problem was inadequate anesthesiologist training in TEE [77]. Adequate training and certification is essential for appropriate patient management.

TEE is a very sensitive indicator of myocardial ischemia, as changes in abnormalities in regional wall motion can be detected almost instantaneously. It is also used for diagnosing right heart failure, left heart failure, left ventricular outflow tract obstruction, intracardiac clots etc. It can be used to monitor pre-existing cardiac pathology such as valvular stenosis and regurgitation, diastolic dysfunction. Certain surgeries mandate use of TEE such as combined heart – liver transplants.

TEE is a very useful tool in diagnosing clots in the heart or pulmonary artery. The estimated incidence of intracardiac thrombosis (ICT) and pulmonary embolism (PE) during LTx is low (1–1.5%), but it has a very high mortality rate (>50%) [78–80]. Acute pulmonary embolism may lead to acute right heart failure (Fig. 2). Recombinant tissue plasminogen activator (rTPA) is used to manage acute pulmonary thromboembolism with hemodynamic decompensation. The doses used are 40 to 100 mg over 2 h [81,82]. Even at low doses, the risk of hemorrhage persists. [82]. There is no evidence-based information regarding a safe and effective dose in the setting of liver transplantation. Low dose recombinant tissue plasminogen activator (0.5–4 mg) administration, however, has been successfully used for treatment of intraoperative thrombosis/embolism during LTx [83]. Systemic thrombosis, is unfortunately, almost always, a fatal event.

TEE is also used for intraoperative management of patients who have dynamic LVOTO during routine evaluation for orthotropic LTx. Interestingly, intraoperative events such as obstruction or outcomes cannot be predicted by the measurement of pressures across the left ventricular outflow tract during dobutamine stress testing. [84]. But a significant LVOT gradient >36 mmHg is a frequent in approximately 40% of patients who have DSE pre-OLT which a has been associated with intraoperative hypotension [85]. TEE is also used for managing patients with HOCM (Fig. 3). Aggravation of mitral regurgitation (MR) due to LVOTO is likely to occur during LTx in cirrhotic patients with HOCM. Moreover, if calcium is administered to treat severe hypocalcaemia, it may induce and aggravate mitral regurgitation in these patients [86].

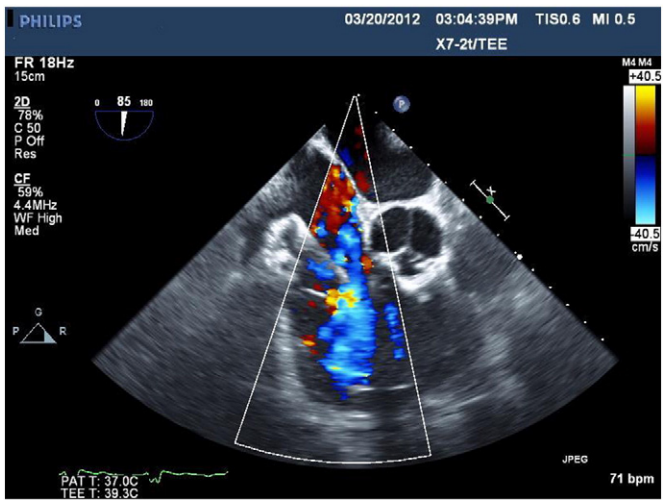

Fig. 2. Massive tricuspid regurgitation due to right heart failure.

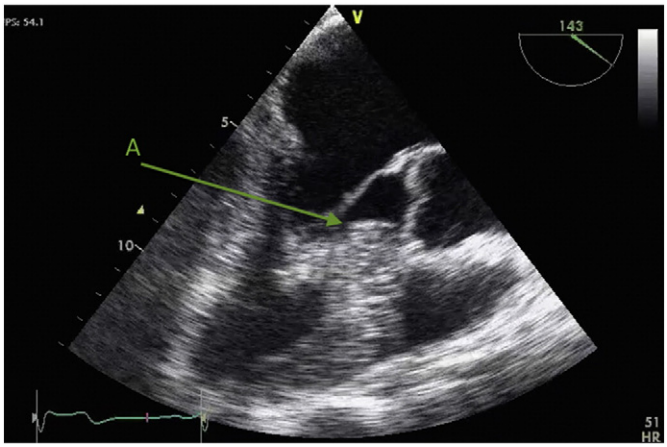

Fig. 3. TEE mid-Esophageal long axis view (ME LAX) showing the anterior leaflet of the mitral valve in close proximity to the hypertrophied septal wall (A) during systole producing left ventricular outflow tract obstruction (LVOTO).

Interventions include institution of veno-venous bypass to avoid acute reductions in preload and titration of esmolol infusions guided by the gradient across the LVOT and SAM. Before reperfusion of the allograft, a phenylephrine infusion maybe started to avoid systemic hypotension directly related to the PRS and to prevent a further decrease in SVR.

TEE has also been used to aid diagnoses of coronary vasospasm and Takotsubo Cardiomyopathy or transient left ventricular apical ballooning syndrome. Takotsubo's cardiomyopathy presents as cardiogenic shock with ST-elevation without angiographic evidence of coronary occlusion [87]. Coronary vasospasm has also been described in liver transplantation, with similar clinical signs resembling an acute myocardial infarction. TEE has been used to diagnose paradoxical air embolism, after a circulatory failure. This allowed early management by hyperbaric oxygen therapy [88]. Intraoperative iatrogenic acute pericardial tamponade diagnosed with TEE has also been reported [89].

Arrhythmias are very common during reperfusion and in the immediate post reperfusion phase. If the patient had a higher baseline K+ and received several red blood cell transfusions, then the likelihood of prereperfusion hyperkalemia was higher. If the graft was a donation after cardiac death (DCD) graft and there was higher baseline K+, the likelihood of early post-reperfusion hyperkalemia was higher [90]. Management of intraoperative arrhythmia and cardiac arrest has been discussed in Table 2.

For intraoperative myocardial infarction, (MI), determine whether the MI is a ST elevation MI (STEMI = ST elevation, new LBBB) or a Non-STEMI (ST depression or dynamic T wave inversion) and accordingly inform the Cardiology/PCI team. A nitroglycerin infusion should be started if there is no RV infarction, and hypotension. Aspirin 325 mg can be crushed and given via the nasogastric tube. It may be prudent to send a set of electrolytes, ABG, troponins and coagulation profile.

The commonest cause for reperfusion cardiac arrest is hyperkalemia. Other causes include hypervolemia, hypoxia, acidosis, hypothermia, tension pneumothorax, tamponade, and pulmonary or cardiac thrombosis. Management of Intraoperative Arrhythmia and Cardiac Arrest has been discussed in Table 2.

Table 2
Management of intraoperative arrhythmia and cardiac arrest.

1. Bradycardias which cause hypotension

Atropine > = 0.5 mg, up to 3 mg. If the bradycardia is refractory, then an epinephrine or dopamine infusion 2–10 mcg kg^{-1} min^{-1} be more effective. Other options include transcutaneous pacing (TCP). TCP is usually indicated in hemodynamically unstable bradycardia, in the setting of acute myocardial infarction (MI) – symptomatic sinus bradycardia, Mobitz type II second degree, third degree heart block, Third degree atrioventricular (AV) block with a wide new QRS complex, new left, right or alternating BBB, bi-fascicular block, bradycardia with symptomatic ventricular escape rhythms.

2. Stable tachycardia

Common intraoperative narrow complex QRS tachycardia <0.12 s are sinus tachycardia, atrial fibrillation, atrial flutter, AV nodal reentry. Most patients with ESLD demonstrate sinus tachycardia intraop. Rates less than 150/min do not need to be treated unless accompanied with hemodynamic instability. For other stable narrow complex tachycardia, use adenosine 6 mg rapid IV push with 20 ml saline bolus via the central line. If there is no conversion, give 12 mg adenosine rapid IV push. Adenosine may cause bronchospasm in patients with asthma. Adenosine increases AV block and will terminate approx. 90% of reentry arrhythmias. It will not terminate atrial flutter nor fibrillation, but slows AV conduction, allowing for identification of flutter or fibrillation waves. Adenosine can also be used for wide complex stable monomorphic VT.

3. Unstable tachycardia

For intraoperative unstable tachycardia such as atrial fibrillation, atrial flutter, reentry supraventricular tachycardia, monomorphic ventricular tachycardia or polymorphic ventricular tachycardia, use synchronized or unsynchronized cardioversion. Synchronization occurs with the R wave. It avoids shock when the heart is vulnerable in which a shock can precipitate VF. Uses lower energy. Unstable Atrial flutter/SVT = 50–100 J, Unstable Atrial Fibrillation = 200 J, Unstable monomorphic VT = 100 J, Unstable Polymorphic VT = defibrillate 360 J. Cardioversion not effective in the treatment of ectopic/multifocal atrial tachycardia, junctional tachycardia because these rhythms have automatic focus, arising from cells that are spontaneously depolarizing at a rapid rate. Delivery of a shock generally cannot stop these rhythms and infact may increase the rate of tachyarrhythmia.

4. Cardiac Arrest: Pulseless Ventricular tachycardia (Vtach)/Ventricular fibrillation (VF)

Start cardiopulmonary resuscitation (CPR)@100/min, with chest compressions at least of 2 inches. Pt should be ventilated with 100% oxygen at the rate of 8–10 breaths/min. Continue CPR while the defibrillator is charging. High quality minimally interrupted CPR is most important. Shock Energy = Monophasic 360 J, Biphasic 120–200 J. For biphasic use manufacturer's recommended or maximum. Shock success is termination of VF for at least 5 seconds following shock. After an initial shock, continue CPR for 2 min. Repeat a rhythm and again shock, followed by CPR for 2 min. And continue the cycle. Administer epinephrine 1 mg IV/IO every 3 min (or vasopressin 40 U IV to replace first or second dose of epinephrine). Give amiodarone 300 mg bolus (second dose 150 mg) for refractory VF/pulseless VT. It is essential to treat reversible causes while performing CPR. MgSO4 1–2 g IV in 10 ml over 5 min should be given for torsades de points.

5. Cardiac Arrest: Pulseless Electrical Activity (PEA), Asystole

These are unshockable rhythms. Start CPR, and administer epinephrine 1 mg IV/IO min or vasopressin 40 IU IV to replace first or second dose of epinephrine. Hypovolemia and hypoxia are the most common causes of PEA. Rhythms in PEA include idioventricular rhythms, ventricular escape rhythms, post defibrillation idioventricular rhythms, sinus rhythm. Atropine is not recommended in management of PEA or asystole.

5. Anesthesia for the living donor

Adult-to-adult living donor LTx (LDLT) is a complex procedure. It can present with serious health risks to the donor. It is essential to establish that the donor voluntarily consent for this procedure and is fully informed of the risks involved.

Preoperative anesthesia evaluation and risk assessment for the donor hepatectomy is essential. Usually, it is preferred that donors have an ASA I or II physical status. The anesthesia management is similar to that of hepatectomy for other diagnosis such as tumors etc. There is a risk of significant blood loss. Large bore intravenous access should be secured and one should be prepared for rapid infusion of colloids, crystalloids and blood products. Extensive resection may disrupt hepatic veins and produce risk of air embolism.

The left lobe, left lobe and caudate, right lobe, extended right lobe and right lateral sector can be used as donor liver grafts [7]. The minimal donor remnant volume should be at least 30% of the original volume. Many surgeons prefer a low central venous pressure to facilitate dissection that minimizes blood loss from the hepatic vessels and vena cava. Maintenance of a low CVP decreases backflow bleeding from the hepatic veins. Low CVP also facilitates safe dissection of the retro-hepatic vena cava and major hepatic veins. Nowadays low CVP is also associated with decrease postoperative morbidity and reduction of hospital stay

[91]. Low CVP anesthesia may cause air embolism, increase requirements for pressor agents and produce postoperative renal dysfunction.

Thoracic epidural analgesia provides excellent analgesia for liver donors [7,92], with catheter insertion at the T6-T9 space. Bupivacaine and Ropivacaine are commonly used local anesthetics. Small amounts of opioids such as fentanyl, sufentanil, hydromorphone or morphine maybe added to the local anesthetic mixture [7,93].

Estimated risk of having serious neurological injury with a neuroaxial block may be as high as 0.08% [94,95]. Pain is more common in lesions affecting nerve roots [96]. The incidence of persistent neurological deficit has been reported as 0.005−0.07% [7,97,98]. The catheter may be kept for a longer time due to persistent pain or transient coagulopathy [99]. The incidence of epidural hematoma is 1:26000 [100] and the risk of epidural abscess is 0.014% [101]. Some donors with thoracic PCEAs experienced more pain as compared to patients who underwent major hepatic resections, probably due to longer surgical duration for donor hepatectomy and neuroplasticity which may have played a role in exaggerated postoperative pain perception along with various psychological factors [7,102].

There maybe several major and minor complications. Approximately 10% of donors had a platelet count < 150,000 × 109/liter, 2–3 years after living donor donation [7,103]. Shoulder pain, pruritus and urinary retention related to epidural morphine were some of the minor anesthestic complications. Major problems included central venous catheter-induced thrombosis of the brachial and subclavian vein, neuropraxia, foot drop and prolonged postdural puncture headache. One of 113 donors died from pulmonary embolism on the 11th postoperative day [7,104].

6. Conclusion

Liver transplantation is a dynamic and professionally challenging field with a touch of altruism. Patients undergoing LTx are at increased risk for both perioperative morbidity and mortality. They can certainly pose significant challenges for intraoperative care for the anesthesiologist.

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