REVIEW ARTICLE

Fifty liver transplants: a single centre experience of haemodynamic management in liver transplantation for cirrhosis [part 1]

B.Gunetilleke[1], R.Ranamuni[1], D.Jayaweera[1], N.Welikala[1], V.Kerner[1], N.Munasinghe[1], R.Withanage[1], N.Wickremasinghe[1], S.Hewage[1], N.Wijesuriya[1], U.Rodrigo[1], A.Mudalige[1], M. Fernando[1], D.Hettiarachchi[2], J.Dissanayake[1], M.Niriella[1], A.Dassanayake[1], R.Wijesuriya[1], C.Liyanage[1] , S.Thilakaratne[1], R.Siriwardana[1], J. De Silva[1]

[1]Colombo North Center for Liver Disease, Faculty of Medicine, University of Kelaniya, Sri Lanka

[2]Faculty of Medicine, University of Colombo, Sri Lanka

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Abstract

Cirrhosis with end stage liver disease (ESLD) is a leading cause of non-communicable disease related deaths in Sri Lanka. Liver transplantation is the only curative treatment for patients with ESLD. The complex multisystem involvement and unique cardiovascular profile characteristic of ESLD present formidable challenges during liver transplantation. Management of the rapid and varied hemodynamic changes during surgery requires an in depth understanding of the physiological effects of each intervention. Based on the current literature and the experience gained at our center during the management of 50 liver transplants, we present optimization strategies and perioperative hemodynamic interventions which we use to 'Fast track' recovery following liver transplantation.

Introduction

In recent years' cirrhosis with end-stage liver disease [ESLD], has been recognized as a leading cause of non-communicable disease-related deaths in Sri Lanka [1]. Nonalcoholic fatty liver disease [NAFLD] and alcohol-related liver disease [ARLD] are the principal cause of ESLD and hepatocellular carcinoma in Sri Lanka [2]. The increase in the prevalence of Non-alcoholic liver disease among urban Sri Lankan adults from 32.6% to 61.5% over 7 years indicates the magnitude of the health care burden [3]. Globally an estimated one million deaths annually are caused by complications of cirrhosis and an additional one million deaths occur due to viral hepatitis and hepatocellular carcinoma [4]. Liver transplantation is the only curative treatment option for patients with end-stage liver disease due to cirrhosis, acute liver failure, certain malignant tumours of the liver, and acute chronic liver failure [ACLF].

Correspondence: Bhagya Gunetilleke
E-mail: bhagya.gun@gmail.com
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The multisystem dysfunction associated with ESLD adds to the complexity of perioperative care in liver transplantation in these patients [5]. With the rising prevalence of diabetes and obesity, the need for liver transplantation is likely to increase dramatically.

At present, only a handful of liver transplants are performed annually in Sri Lanka [2]. There is a dire need to develop a sustainable liver transplant program in the country. This requires a commitment from multiple stakeholders including the state and the health care workers. Developing the legal framework, infrastructure, organ procurement process and multidisciplinary human resources for such a transplant program requires much foresight and a broad vision. Subspecialties related to transplant surgery and medicine are already well established in Sri Lanka. Considering the key role of the anaesthetist in the multidisciplinary transplant team, the training program leading to board certification of specialist anaesthetists with a special interest in Transplant Anaesthesia and Critical care was established by the Board of Study in Anaesthesiology, Postgraduate Institute of Medicine, University of Colombo in 2018.

1. Evolution of liver transplant surgery

The first successful orthotopic human liver transplant surgery was carried out in 1963 on a child with biliary atresia at the University of Colorado, USA, by a team led by Thomas Starzl, surgeon and Tony Aldrete, anaesthetist - a legendary duo. The protocols developed for renal transplantation and immune suppression were adapted for liver transplantation. The liver transplant failed due to a massive intraoperative haemorrhage. Repeated failures prompted a self-imposed moratorium. After much research on animal models, the transplant program recommenced [6]. The impressive progress made in the field of liver transplantation since then has been made possible due to advances in the fields of surgery, anaesthesia, critical care, hepatology, immune suppression, coagulation management, nursing, and the evolution of machine perfusion [7]. Currently, almost thirty thousand liver transplants are performed globally every year.

In Sri Lanka, the first successful cadaveric liver transplant was carried out in 2010 [8]. The team from the Colombo North Centre for Liver disease carried out the first live donor liver transplant in 2012 followed by the first liver transplant for acute liver failure in 2017 [9]. In 2018 the first liver transplant without using blood products was 'fast tracked'[10]. The same team performed the first successful paediatric live donor liver transplant in 2020 [11].

2. Grading of End-stage liver disease and selection for transplant

Globally, a liver transplant is hampered by a shortage of donor organs. Donor liver grafts that would have been considered unsuitable previously are now being utilized with an excellent outcome. To overcome the shortage of organs, an equitable, needs-based allocation system was developed.

The Child-Pugh-Turcotte score has limited use for prioritizing patients for liver transplants [12, 13]. The introduction of the Model for End-Stage Liver Disease [MELD] score in 2002, followed by the MELDNa score provided an objective ranking system of potential recipients and a transparent system for allocation of donor organs [14, 15]. The utility of a frailty score to further shorten waitlist time is under consideration. The Paediatric End-Stage Liver Disease [PELD] score is used to predict waitlist mortality and to prioritize children with ESLD awaiting liver transplantation [16]. The mean MELD score at the time of listing for liver transplantation at the Colombo North Centre for Liver Disease [CNCLD] in 2017 was 17 and scores ranged from 15-20 [17]. A cirrhotic with a MELD score of less than 14 is usually not listed for liver transplantation since the risk associated with liver transplants outweigh the benefit.

3.Organ dysfunction in ESLD and impact on haemodynamics

Organ dysfunction and deterioration of quality of life in cirrhotics are typically relentless; progressing from a compensated stage to early and late decompensated cirrhosis [18]. Decompensated cirrhosis carries a dismal prognosis without liver transplantation [19]. Acute chronic liver failure [ACLF] in cirrhotics is characterized by the presence of acute multiple organ failure typically triggered by alcohol consumption or infection. The severity of multi-organ involvement in ACLF is defined by the CLIF-Consortium [C] ACLF score [18]. The indications for a liver transplant in acute liver failure and ESLD are well defined. The underlying pathophysiology of multi-organ dysfunction stems from deranged hepatocellular synthetic, immune, and metabolic clearance and portal hypertension. Dysfunction of *Kupffer* cells contributes to impaired immune function. Deranged flow dynamics in hepatic sinusoids, angiogenesis and nitric oxide-dependent vasodilatation contribute to elevated portal venous pressure and portosystemic shunt [13, 20]. Ischemia resulting from thrombosis of the portal vein could prime the tissues for ischemia-reperfusion injury in the setting of liver transplantation [21].

4.Cardiovascular Assessment

Cardiac risk management by the anaesthetist is vital for the success of a liver transplant. Acute perioperative changes superimposed on deranged cardiopulmonary function, systemic, pulmonary, and portal circulation and coagulation, can result in a life-threatening haemodynamic disturbance in the perioperative period. Cardiopulmonary complications are a principal cause of death in the perioperative period. Metabolic syndrome and asymptomatic moderate coronary artery stenosis are common in patients with NAFLD listed for liver transplantation. The presence of Nonalcoholic steatohepatitis [NASH] and renal dysfunction are predictors of critical coronary stenosis. Appropriate pre-transplant coronary revascularization can reduce perioperative haemodynamic instability and mortality associated with coronary artery disease [22]. Cytokines especially TNF-α contribute to nitric oxide overproduction in the splanchnic arterial circulation in ESLD [20]. This chronic vasodilatory state may mask underlying cardiac dysfunction. The limited coronary flow reserve could contribute to the increased risk of acute perioperative cardiac events.

Cirrhotic cardiomyopathy is characterized by the blunted inotropic and chronotropic response to stress, altered diastolic relaxation and electrophysiological abnormalities including QT interval prolongation. Cirrhotic cardiomyopathy usually resolves following liver transplantation. An ejection fraction of 40% is considered the minimum required for a liver transplant [22]. Porto-pulmonary hypertension is associated with portal hypertension in ESLD. The risk of right ventricular failure particularly during reperfusion needs to be considered. The reversibility of raised pulmonary arterial pressure, pulmonary vascular resistance and control of mean right atrial pressure are important determinants of the outcome following a liver transplant [23]. An irreversible mean pulmonary arterial pressure exceeding 40mmHg is considered a contraindication for liver transplantation in our unit. Non-invasive investigations for assessment of ischemic heart disease in candidates for liver transplant is of limited value. Though the inability to achieve the target heart rate is limited due to impaired chronotropic, exercise stress testing and dobutamine stress echocardiography provides useful information regarding the existence of inducible ischemia and left ventricular outflow tract obstruction associated with cirrhosis [24]. A reduced aerobic capacity on cardiopulmonary exercise testing is a predictor of poor outcome following liver transplant [25]. The 6-minute walk test [6MWT], which is easily performed even in low resource

settings, is a predictor of cardiac and pulmonary outcome in the perioperative period. A 6-minute walk distance of fewer than 250 meters is associated with an increased risk of waitlist mortality in liver transplant candidates. An improvement in 6MWT distance translates to improved survival [26].

The 6MWT has been included as a screening test in our preoperative assessment protocol. Invasive coronary angiography can be carried out despite the presence of renal dysfunction and the risk of bleeding [27]. In our unit, potential recipients with renal dysfunction undergo multidisciplinary risk assessment with input from nephrology, cardiology, and transplant team to determining the utility of coronary angiography. The use of dual antiplatelet therapy in the perioperative period is described in case reports. In the absence of specific recommendations, the unit guideline reflects the guidance relating to the use of dual antiplatelet therapy in major abdominal surgery [28].

5. Phases of liver transplantation surgery and haemodynamic management

Pre-anhepatic phase

During this phase surgeons painstakingly ligate intraperitoneal varices and prepares for the explant of the native liver. Compression of the inferior vena cava due to manipulation of the liver, drainage of ascites, incessant blood loss due to portal hypertension and cirrhotic coagulopathy contribute to significant hypotension. A central venous pressure below 5mmHg is targeted to minimize blood loss due to venous backflow. The use of the rapid fluid infuser-warmer and forced air warmers helps to maintain normothermia. Severe coagulopathy, acidosis, hypoglycemia and bacteremia are potential complications during this phase. Optimal hemostatic therapy guided by viscoelastic testing [VET] is possible only when a point of care testing facility is available in the theatre. Careful titration of intravenous fluid and vasopressors is required to counter hypotension due to cross-clamping of the portal vein and the inferior vena cava at the onset of the anhepatic phase [29, 30].

Anhepatic phase

Cross clamp of the portal vein, the hepatic artery, side clamping of the inferior vena cava and explant of the liver marks the onset of the anhepatic phase. The use of the 'Piggyback' technique is associated with less haemodynamic instability than the 'caval replacement' technique. Porto-caval shunts and veno-venous bypass are utilized to decompresses the splanchnic circulation and to achieve haemodynamic stability in selected patients. Progressive lactic acidosis, coagulopathy and hypoglycemia characterize this phase. Coagulopathy is monitored with VET. Though a decline in plasma fibrinogen is commonly observed during this phase, correction is not warranted in the absence of significant bleeding. Cryoprecipitate or factor concentrates are used to restore hemostasis in the presence of bleeding and abnormalities in VET. Fluid loading in anticipation of sudden haemorrhage could lead to congestion of the inferior vena cava, impaired hepatic outflow, congestion and dysfunction of the grafted liver. Under filling contributes to the relative hypovolemia and hypotension at reperfusion. Goal-directed use of intravenous fluids, vasopressors, inotropes, calcium, VET guided optimization of coagulation and correction of metabolic derangements during the anhepatic phase are aimed at minimizing haemodynamic derangement at reperfusion [29, 30].

Reperfusion and neo hepatic phase

This phase begins with reperfusion of the graft with the restoration of blood flow in the inferior vena cava and portal vein. Reperfusion hypotension is defined as a 30% drop of baseline mean arterial pressure, lasting more than a minute within five minutes of reperfusion. Severe haemodynamic instability during the reperfusion phase could be protracted and is usually due to a prolonged anhepatic phase, poor graft quality, preservation injury of graft and ischemia and reperfusion injury. Impaired cardiac contractility, arrhythmia, coagulopathy and bleeding, acidosis and hyperkalemia contribute to the instability. Multiple organ dysfunction mediated by inflammatory mediators and reactive oxygen species could result from reperfusion injury. Coordination between the anaesthetist and surgeon is vital to control the degree of hypotension at reperfusion. Calcium gluconate, boluses of adrenaline, blood products and intravenous fluids are used to restore stability. Haemodynamic stability and satisfactory graft function permit rapid weaning of vasopressors and inotropes and the resolution of lactic acidosis, coagulopathy and production of bile [29, 30].

Sustained hypotension with a mean arterial pressure [MAP] below 50 mmHg and fluctuation exceeding 25% of baseline MAP are independent haemodynamic predictors of 30-day mortality and graft failure [31]. Anticipating haemodynamic changes unique to each phase and intervening appropriately to mitigate the haemodynamic instability is vital to ensure a good outcome.

The haemodynamic management for liver transplantation carried out at the Colombo North Centre for Liver Disease will be discussed under the following headings in part 2 of this article [Volume 3 Issue 39].

1.Haemodynamic monitoring

2.Intravenous fluids

3.Haemodynamic management

4.Rebalanced Coagulation in cirrhosis and assessment of hemostasis

5.Transfusion of blood products

6.'Fast track' recovery

7.Lessons learnt

8.Annexure 1 - The guidance on haemodynamic management in Liver transplantation at the Colombo North Centre for Liver Disease

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