Optimizing Intraoperative Haemodynamics and Haemostasis to Enhance Recovery After Liver Transplantation for Cirrhosis in Adults

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Cirrhosis with end stage liver disease is a leading cause of non-communicable disease related deaths in Sri Lanka. Liver transplantation remains the only curative treatment for such patients. Multi-organ dysfunction characteristic of end stage liver disease, surgical and anaesthetic factors, quality of the graft, coagulopathy and haemodynamic instability, all lead to the complexity of the perioperative care for liver transplant. Aggressive management focused particularly on maintaining intra-operative haemodynamic stability and optimising haemostasis, directly impacts successful patient outcomes and forms the core of the anaesthetic strategy.

Key words: Optimisation, Haemodynamics, Haemostasis, Enhanced Recovery, Liver Transplant, Cirrhosis

Introduction

Cryptogenic cirrhosis and alcoholic cirrhosis are principle causes of end stage liver disease (ESLD) in the majority of adults listed for liver transplantation (LT) at the Colombo North Center for Liver Diseases (CNCLD) [1]. Non Alcoholic steatohepatitis (NASH), a more severe form Non-alcoholic fatty liver disease (NAFLD) is thought to be the predominant cause of cryptogenic cirrhosis.

Haemodynamic instability (HDI) is commonly encountered in patients with ESLD and is the result of a complex interplay of numerous pathophysiological factors.

The incidence of coronary artery disease and impaired myocardial performance is common among such patients, and the combination of a preoperative ejection fraction less than 50%, prolongation of the QT interval, and diastolic dysfunction is strongly suggestive of underlying cirrhotic cardiomyopathy.[2,3] Right ventricular dysfunction seen in ESLD is usually associated with porto-pulmonary hypertension. Excess splanchnic nitric oxide production with profound systemic and splanchnic vasodilatation and sequestration of blood within the splanchnic circulation leads to a state of relative hypovolemia, systemic hypotension, and organ hypoperfusion. Intraoperatively, rapid drainage of ascites, bleeding, vasodilatation, and surgical maneuvers including varying degrees of clamping of the portal vein and inferior vena cava cause a reduction in the cardiac preload and HDI. Arrhythmia, ventricular dysfunction, and a further drop in SVR is often witnessed secondary to ischemia reperfusion injury (IRI). This vasoplegic state may progress to a state of refractory hypotension unresponsive to vasopressors. The severity of IRI is directly impacted by graft quality, length of ischemic time and degree of graft preservation injury.[3] Intraoperative HDI is closely linked to adverse

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Received: 22/05/2022
Accepted: 01/06/2022

DOI: http://doi.org/10.4038/slja.v30i1.9070

outcomes of early graft dysfunction, renal failure, myocardial ischaemia and death. [3-8]

Given the high risk and complexity of the management, enhanced recovery after surgery (ERAS) protocols have been developed to improve outcomes following LT. Such protocols are delivered by Integrated Delivery Systems (IDS) whereby multiple clinical teams communicate and coordinate the delivery of optimal patient care throughout a patient's perioperative journey. [9,10]

Intra-operatively, such ERAS protocols incorporate multiple evidence-based interventions including advanced haemodynamic monitoring, restrictive use of intravenous fluid, and viscoelastic assay guided management of haemostasis. Whilst demonstration of a direct beneficial effect of ERAS in complex procedures such as liver transplant is difficult due to multiple confounding factors including severity of recipient illness and graft quality, impressive outcomes have been demonstrated by teams adopting ERAS protocols in liver transplant. Such protocolized interventions have enabled early extubation, avoidance of postoperative ventilation, early mobilization, reduction in postoperative complications, shortened length of intensive care and hospital stay and reduced cost of LT, even in patients with high Model for End stage Liver Disease (MELD) scores. [9,10]

Optimising Haemodynamics

i) Haemodynamic monitoring

Early identification of factors predisposing to HDI is key to effective intervention. Invasive arterial blood pressure and central venous pressure, urine output, blood gases, biochemistry including lactate and electrolytes, and haemostasis are monitored during surgery. Mixed venous oxygen saturation, though traditionally used as a measure of the oxygen supply-demand balance, correlates poorly with cardiac output in cirrhotics. Given the compromised state of the patient and rapid and potentially lethal cardiovascular derangement experienced during LT, advanced haemodynamic monitoring is mandated.

The pulmonary artery catheter (PAC) provides an array of useful hemodynamic data and is particularly useful in managing patients with porto-pulmonary hypertension.[3]

Trans-oesophageal echocardiography (TOE) is increasingly used owing to its versatility in providing real-time information on i) intra-cardiac flow, volume and pressure, ii) cardiac structure, function and wall motion abnormalities, and ii) embolic material and intracardiac thrombus, information not readily available with other haemodynamic monitors[11]. The inability to measure rapid changes in pulmonary and systemic vascular resistance are significant limitations of TOE. Alternative technologies for measuring cardiac output include calibrated, pulse wave analysis e.g. PiCCO (Pulse index cardiac output) and LiDCO (Lithium dilution cardiac output). The utility of uncalibrated pulse wave analysis-based monitors e.g., Flowtrac, in cirrhotics is limited as rapid changes in vascular resistance and the use of vasoactive drugs limits their accuracy. Access to advanced haemodynamic monitors is often limited due to cost in a resource poor setting. This restricts the ability to implement a uniform monitoring protocol.

ii) Haemodynamic management

The three phases of a liver transplant - dissection, anhepatic and reperfusion phases, are each unique in their pathophysiology and thus require tailored management strategies. A restrictive fluid strategy, where volume administration is triggered by volume responsive HDI, is associated with reduced hepatic and portal venous pressure and intraoperative bleeding, pulmonary complications, duration of post-operative ventilation, length of ileus, and length of ICU stay. Vasopressors are an integral component of a restrictive fluid strategy. The evidence to support an association between a restrictive fluid strategy and early acute kidney injury or the need for renal replacement therapy in LT is not robust [3,12-16]. Targets for stroke volume variation, stroke volume and cardiac index are targeted using a minimum volume of fluid. A CVP of less than 5mmHg is targeted to minimise bleeding

associated with hepatic congestion and to reduce portal venous pressure[15]. The 'Piggy-back technique' is the preferred surgical technique at CNCLD as in our experience it causes less HDI than cross clamp of the inferior vena cava. Veno-venous bypass may also be used to overcome severe HDI associated with the above techniques.[3]

iii) Intravenous fluid

Balanced salt solutions are the preferred crystalloid in LT. Use of solutions with a high sodium content in the presence of hyponatraemia can result in dangerous fluctuations of serum sodium concentration[17]. The metabolism of both acetate and lactate by the liver is compromised during LT.

Myocardial depression and HDI are adverse effects of buffered acetate solutions, though the impact on outcome when used in LT unclear[18]. Plasma acetate assay is not readily available unlike for lactate.

Compound sodium lactate has the potential to elevate serum lactate in ESLD. In donor hepatectomy its use is associated with higher lactate, peak total bilirubin concentration, a prolonged prothrombin time and lower albumin concentration without a significant adverse impact on the final outcome when compared to balanced acetate solutions.[19]

Compound sodium lactate is the crystalloid of choice for adult liver transplantation at CNCLD. Normal saline is preferred over ringers lactate in paediatric LT [20].

Whilst albumin effectively expands intravascular volume with minimal effect on portal venous pressure, crystalloids have been shown to be superior to 5% albumin based fluid regime in live donor liver transplantation[21]. At CNCLD albumin is used as a replacement fluid in LT particularly after drainage of large volumes of ascites in the dissection phase or in the presence of a steep rise in serum lactate [3]. A plasma albumin above 25 g/l is targeted until the hepatic synthesis of albumin is restored; usually seen around the third postoperative day[22]. Synthetic starch colloid solutions are not recommended in the critically ill due to the risk of renal injury and a non-significant but nevertheless increased risk of bleeding when compared to compound sodium acetate. [23]

All intravenous fluids are administered through a 'Rapid infuser-warmer'. This device permits administration of fluid at 37^{o}C at rates of up to 750ml/minute with inbuilt pressure and air detection systems, while tracking the volume of fluid infused.

iv) Vasopressors

Restrictive use of intravenous fluid is associated with a degree of dependence on vasopressors to maintain haemodynamic stability. Such a strategy is associated with a lower blood loss, fewer pulmonary complications, shorter duration of ventilation and ICU stay. The impact of intraoperative use of vasopressor on post LT, acute kidney injury (AKI) and need for renal replacement therapy (RRT) is not well defined. [16,24]

At CNCLD, Noradrenaline (NE) is used as the first-line vasopressor. [3] Vasopressin is synergistic with NE, and is usually added as the second-line vasopressor when NE dose exceeds 0.1 µg/kg/min. Because of the low endogenous vasopressin levels in ESLD, addition of vasopressin helps to 'centralise' blood volume and is particularly useful in managing vasoplegic shock during LT[3,25,26]. The splanchnic vasoconstrictors Terlipressin, is used for the intraoperative treatment of portal hypertension and small for size graft syndrome [3] .

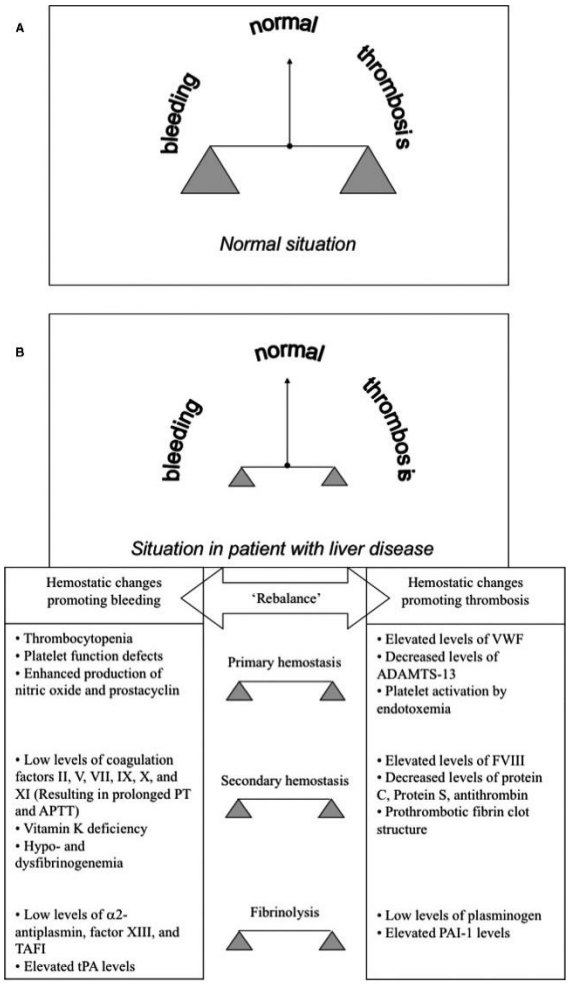
Though the use of vasopressors in the presence of preoperative renal dysfunction and postoperative anemia have been identified as a predictor of early post LT renal dysfunction, this relationship might reflect the severity of underlying cirrhosis and organ dysfunction. [24]

v) Inotropes

Ventricular dysfunction is a feature of cirrhotic cardiomyopathy and is commonly observed during the reperfusion stage. Inhaled nitric oxide, prostacyclin and intravenous milrinone are used to treat right ventricular dysfunction secondary to porto-pulmonary hypertension. At CNCLD dobutamine is the inotrope of choice. A cardiac

function index (CFI) on PiCCO of less than 5.5% is used as a trigger for initiating a dobutamine infusion. Good graft function usually enables rapid tailing of dobutamine in the post reperfusion phase.

Figure 1. Deranged hepatic synthesis and rebalancing of pro, anti-coagulant and fibrinolytic, anti-fibrinolytic mechanism in cirrhosis - The concept of rebalanced haemostasis in patients with liver disease **[27].**



Optimising Haemostasis

(i) Rebalanced coagulation with reduced reserves, utility of standard tests of coagulation and viscoelastic hemostatic tests

Traditionally, patients with chronic liver disease were thought to have a coagulopathy with an increased risk of bleeding as a consequence of reduced synthesis of clotting factors. Recent evidence suggests that such patients are actually in a dynamic state of 'rebalance' due to deranged primary and secondary haemostasis, anticoagulation and fibrinolysis and a 'reduced reserve' due to a reduced hepatic synthesis (Fig 1) [27]. In ESLD , this precarious balance can easily be disturbed by stressors including liver failure, surgery, bleeding and infection.

Standard tests of coagulation such as prothrombin, activated partial thromboplastin time, platelet count and fibrinogen assay have limited use as predictors of the haemostatic status and bleeding risk in cirrhotics.

- Effect of thrombocytopenia secondary to splenic sequestration and impaired hepatic thrombopoietin synthesis is counter balanced by increased levels of Von Willebrand factor (VWF) and reduction of VWF cleavage protein ADAMTS-13 predisposing to thrombosis [27].
- Prothrombin time (PT) / International normalized ratio (INR) which are minimally affected by changes in levels of protein C and S tends to overestimate bleeding risk. Correction of coagulopathy with fresh frozen plasma (FFP) based purely on PT/INR results in over correction, hypercoagulability and fluid overload. [27]
- Abnormalities of fibrinolysis are not readily detected by standard tests of coagulation. Hyperfibrinolysis during the dissection phase is usually pathological and needs to be treated while hyperfibrinolysis in the anhepatic and reperfusion phase is usually self-limiting.

Whole blood point of care viscoelastic haemostatic assays (VHA); Thromboelastography (TEG) and Rotational thromboelastometry (ROTEM) are increasingly utilized to assess the state of clot formation, strength and fibrinolysis within a short turnaround time and guide therapy in patients with ESLD. VHA reliably predict bleeding and need for transfusion[4,28] . At CNCLD, the management of bleeding and coagulopathy during LT is based on clinical assessment and the Essen University A5 protocol. A modified timing schedule for testing is utilized at CNCLD due to

the lack of point of care testing in the theatre and ICU [4,28].

(ii) Transfusion of blood products

Blood product transfusion exposes the patient to numerous risks including transfusion reactions and immune modulation. Hypervolaemia and increase in portal hypertension increases bleeding in LT. Anaemia as well as transfusion of blood products have been linked to post liver transplant AKI [24].

Red cell transfusion is an independent risk factor for early post LT AKI and the number of units of packed red cells correlates with reduced one year survival following LT[29-33].

Platelet transfusion is a risk factor for acute lung injury, graft injury and correlates strongly with poor post-transplant outcome [29,34-36]. The use of FFP in LT needs careful consideration due to concerns regarding its safety and limited of evidence of benefit particularly when thrombin generation is impaired [4,31].

A better understanding of pathophysiology of anaemia and coagulopathy in ESLD as well as advances in surgery, anaesthesia and VHA guided coagulation therapy have revolutionised the management of coagulopathy and bleeding induced HDI in LT and led to a dramatic reduction in transfused volumes of blood products [4,29,30].

At CNCLD, leukocyte depleted red blood cells are transfused targeting a Hb of 7-9g/dl. The use of tranexamic acid, cryoprecipitate, platelet concentrate and FFP is guided by the Essen University A5 protocol. [(4)] The use of factor concentrates reduces the exposure to blood products [(34,37)], but its use at CNCLD is limited due to cost.

A restrictive transfusion strategy linked to VHA based protocols are integrated in ERAS protocols in liver transplantation.[(38,39)]

CONCLUSION

End stage liver disease secondary to cirrhosis is a leading cause of death due to non-communicable disease in Sri Lanka. Cryptogenic cirrhosis and alcoholic cirrhosis are the principal aetiologies in patients presenting for liver transplant at CNCLD. Management of haemodynamics and haemostasis in liver transplant is complex due to multiple factors including ESLD related multisytem dysfunction, and graft quality. A strategy targeting haemodynamic stability and optimal haemostasis is critical to achieve enhanced recovery following liver transplant.

Key points

- Multiple factors including liver failure, portal hypertension, coagulopathy, multisystem dysfunction, graft related factors compounded by stresses induced by surgery and anaesthesia contribute to HDI.
- Advanced haemodynamic monitoring, restrictive intravenous fluid strategy combined with vasopressors and inotropes are used to manage HDI.
- Rebalanced coagulation with diminished reserves results in a unique cirrhotic coagulopathy.
- Use of a VHA based algorithm has resulted in a drastic reduction of blood product use without an increase in bleeding or thrombosis.
- Adoption of ERAS protocols in LT have been linked to improved outcome.

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