REVIEW ARTICLE

Fifty liver transplants: a single centre experience of haemodynamic management in liver transplantation for cirrhosis [part 2]

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Abstract

Globally, an estimated one million deaths occur annually due to complications of cirrhosis. Cirrhosis with end stage liver disease [ESLD] is a leading cause death due to non-communicable diseases in Sri Lanka. Non-alcoholic fatty liver disease [NAFLD] and alcohol related liver disease [ARLD] are the principal causes of ESLD due to cirrhosis in Sri Lanka. Liver transplantation remains the only curative treatment for such patients. Multiorgan dysfunction and hemodynamic instability characteristic of ESLD adds to the complexity of perioperative care in liver transplantation. Maintenance of stable hemodynamics including optimal hemostasis forms the core of the anaesthetic strategy in liver transplantation.

1. Introduction

Advances in hemodynamic management have contributed significantly to excellent outcomes following liver transplantation for ESLD in high volume centers. Despite limited resources the team at CNCLD strives to adopt an evidence-based approach to haemodynamic management in liver transplant. This approach coupled with innovation and perseverance have been key factors which enabled the team at CNCLD which carried out the first liver transplant in 2011, achieve the milestone of fifty liver transplants in 2020..

2. Haemodynamic monitoring

Haemodynamic instability [HDI] during liver transplant [LT] is a risk factor for major adverse cardiovascular events, graft dysfunction and death. Multiple factors including fluctuations in cardiac preload, contractility, afterload, arrhythmia, electrolyte disturbance, and factors related to the graft result in HDI.

Monitoring of invasive arterial and central venous pressure, urine output, blood gases, lactate, electrolytes, and coagulation supplemented by advanced hemodynamic monitoring is essential to identify and treat HDI during LT.

The pulmonary artery catheter [PAC] remains a valuable tool particularly in patients with porto-pulmonary hypertension . Mixed venous oxygen saturation though traditionally used as a measure of oxygen supply-demand balance, correlates poorly with cardiac output in liver transplantation.

Trans-esophageal echocardiography [TEE] is used owing to its versatility in providing real-time information on intra cardiac flow, volume and pressure, structure, function, and the presence of embolic material. This information is not readily available with other types of haemodynamic monitors. The inability to measure rapid changes in pulmonary and systemic vascular resistance are significant limitations of TEE. Access to PAC and TEE at CNCLD is limited by cost and logistical factors.

Calibrated pulse wave analysis based hemodynamic monitors e.g., PiCCO [Pulse index continuous cardiac output], LiDCO plus [Lithium dilution cardiac output] provides clinically useful information in the setting of LT. Rapid changes in vascular resistance and the presence of vasoactive drugs in LT, limits the usefulness of uncalibrated pulse wave analysis-based monitors including Flowtrac®. Esophageal Doppler cardiac output monitor is a useful adjunct to other advanced haemodynamic monitors in stable cirrhotics . Due to limited resource a combination uncalibrated cardiac output monitors, Flowtrac® or LiDCO rapid® and esophageal doppler are used to guide hemodynamic therapy for LT at CNCLD. Delays in procuring disposables limits our ability to use a uniform monitoring protocol.

3. Haemodynamic management

Specific strategies are required to manage hemodynamic derangement unique to the pre-anhepatic [dissection], anhepatic and reperfusion phases. A goal directed strategy targeting volume responsiveness, cardiac output and stroke volume is associated with a less positive fluid balance, reduced duration of post-operative ventilation and reduced length of ileus . A restrictive fluid strategy combined with vasopressors, facilitates low central venous pressure [CVP], reduction of portal venous pressure, intraoperative bleeding,

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pulmonary complications, duration of ventilation and length of ICU stay . The haemodynamic strategy adopted at CNCLD aims to achieve haemodynamic goals utilizing the minimum volume of intravenous fluid and blood products in combination with vasopressors and inotropes.

4. Intravenous fluid

The potential benefits of a restrictive fluid management strategy in LT are well recognized . Balanced salt solutions are the preferred crystalloid in LT . Solutions with a high sodium content should be used with caution as fluctuation of serum sodium concentration in the hyponatremic cirrhotic could result in osmotic demyelination. Metabolism of both acetate and lactate by the liver is compromised during liver transplantation. The lack of data relating to the use of buffered acetate containing balanced solutions in LT, the risk of acetate induced myocardial depression and the inability to assay acetate, limits the use of buffered acetate solutions in liver transplantation . Use of compound sodium lactate solutions in donor hepatectomy is associated with higher lactate, peak total bilirubin concentration, a prolonged prothrombin time and lower albumin concentration when compared to those treated with acetate containing solutions. These changes attributed to compound sodium lactate however did not result in an increase in complications or a prolonged hospital stay .

Compound sodium lactate solutions should be used with caution in pediatric recipients of live donor liver grafts until further evidence becomes available regarding its safety in comparison to normal saline . Compound sodium lactate is the crystalloid of choice for adult liver transplantation at CNCLD. Hourly blood gas analysis permits close monitoring of lactate. When compared with an albumin-based regime, crystalloid use in live donor liver transplant [LDLT] is associated with better outcomes .

5% albumin is widely used as a replacement fluid in liver transplant. Albumin a molecule critical to the integrity of the endothelial glycocalyx, expands intravascular volume with minimal effect on portal venous pressure. This fluid however, may contribute to albumin shift out of the intravascular compartment.

At CNCLD, 5% albumin is used if a large volume of ascitic fluid is drained in the dissection phase, if large volume crystalloid use is anticipated and in the presence of a steep rise in serum lactate precluding the use of compound sodium lactate. A plasma albumin above 25 g/l is targeted until the hepatic synthesis of albumin is restored, usually around the third postoperative day .

The use of synthetic starch colloid solutions in critically ill patients has been associated with an increase in the need for renal replacement therapy . The use of synthetic starch solutions in liver transplant is not widespread in the absence of robust evidence regarding its safety in this setting.

At CNCLD, all intravenous fluids are infused via a rapid infuser which delivers fluid at 37^{o}C, at rates of up to 750ml/minute. Inline volume and pressure monitors and air detection systems are useful safety features incorporated in this device.

5. Vasopressors

Restrictive use of intravenous fluid results in greater dependence on vasopressors to maintain hemodynamic stability. Though the use of vasopressors, preoperative renal dysfunction and postoperative anemia have been identified as predictors of early post LT renal dysfunction, this relationship may reflect severity of underlying ESLD and the requirement for vasopressors rather than causality .

Terlipressin, a splanchnic vasoconstrictor improves renal perfusion, reduces the risk of post-operative acute kidney injury [AKI], small for size graft syndrome and is used in the management of portal hypertension .

Vasopressors have a volume sparing effect. This results in a lower fluid balance at the end of LT. This is true even of older patients with higher MELD scores, larger blood loss, given greater volumes of blood products. A reduced positive fluid balance was associated with a lower incidence of postoperative acute kidney injury; shorter duration of ventilation and ICU stay . In patients with a positive fluid balance, use of vasopressors reduced the need for renal replacement therapy and improved 1 year mortality. Noradrenaline [NE] is preferred to dopamine, adrenaline, and vasopressin as the first line vasopressor. The low endogenous vasopressin levels in ESLD results in a rapid response to exogenous vasopressin. Vasopressin is useful in managing the vasoplegic syndrome, which occurs predominantly in the reperfusion phase of liver transplantation.

Vasopressin is synergistic with NE and is added when NE dose exceeds 0.1 μg/kg/min .

Hemodynamic management for liver transplantation at CNCLD is outlined in 'Guide to Hemodynamic Management in Liver Transplantation-CNCLD [Annexure 1].

6. Inotropes

The combination of a preoperative ejection fraction less than 50%, prolongation of QT interval and diastolic dysfunction is strongly suggestive of underlying cirrhotic cardiomyopathy. Left and right ventricular dysfunction are common, particularly during reperfusion. Dobutamine is the inotrope of choice at CNCLD. Inhaled nitric oxide, prostacyclin,

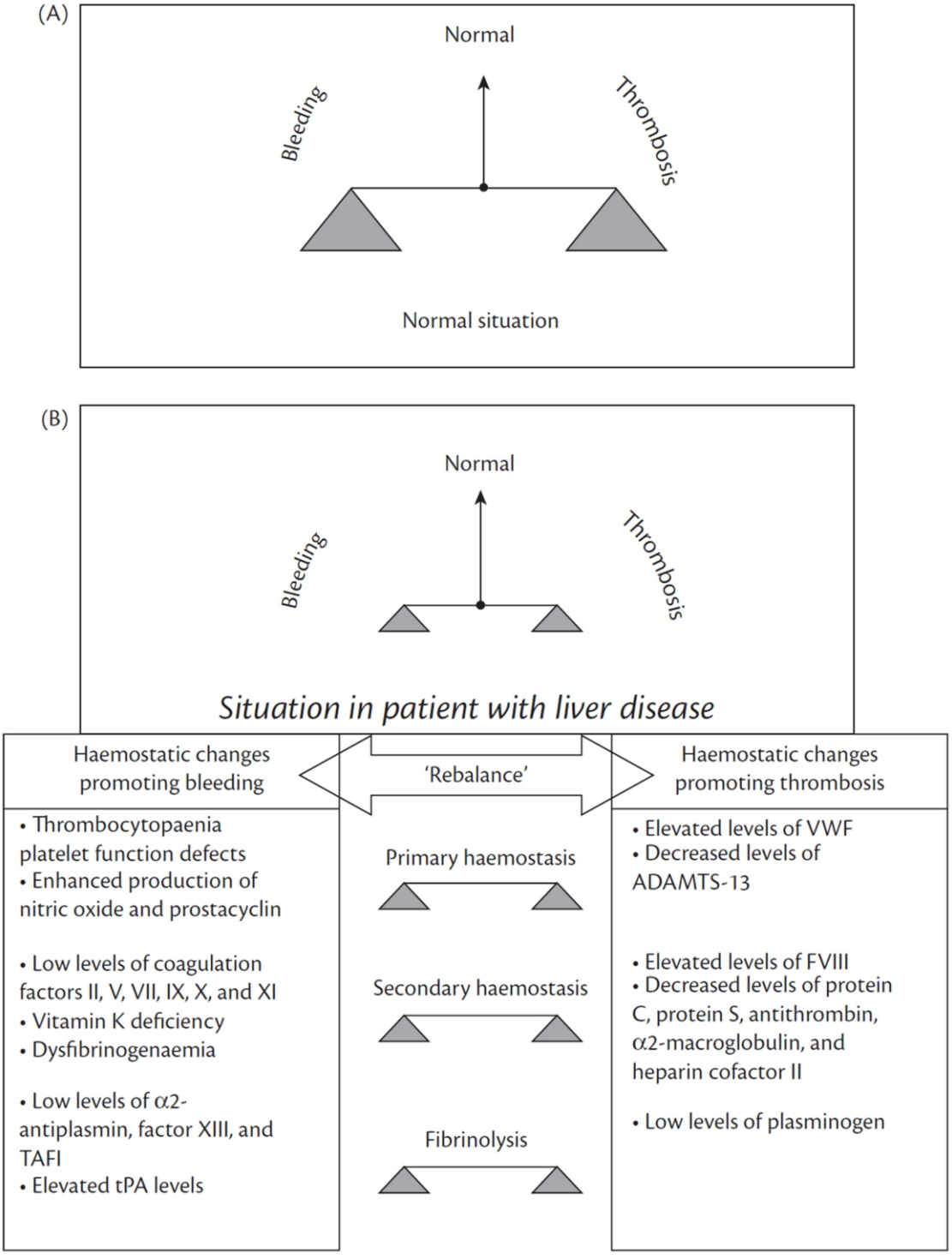

Figure 1. The concept of rebalanced hemostasis in patients with liver disease: Communication from the ISTH SSC working group on hemostatic management of patients with liver disease.

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intravenous milrinone and extracorporeal membrane oxygenation [ECMO] have been used to treat porto-pulmonary hypertension.

7. Rebalanced hemostasis and management of coagulation

Chronic end stage liver disease is characterized by derangements in primary and secondary hemostasis and fibrinolysis [Figure 1].

ESLD is characterized by re-balanced hemostasis with reduced hemostatic reserve [Fig 1]. This precarious balance could tilt to a hyper or hypocoagulable state induced by stressors including surgery, infection, or ischemia-reperfusion injury. Standard tests of coagulation; platelet count, prothrombin time [PT], activated partial thromboplastin time [APTT] and fibrinogen levels are of limited value in complex acquired disorders of hemostasis as seen in ESLD. PT is unaffected by changes in levels of protein C and S. Use of PT and INR to guide correction of coagulopathy in ESLD results in over correction of coagulopathy.

Increased levels of Von Willebrand factor [VWF] and reduction of VWF cleavage protein ADAMTS-13 predisposes to thrombosis despite thrombocytopenia [18].
Hyperfibrinolysis is not readily detected by standard tests of coagulation. Hyperfibrinolysis during the pre-anhepatic phase and fulminant hyperfibrinolysis with diffuse bleeding in the anhepatic and reperfusion phases should be treated with antifibrinolytics. Hyperfibrinolysis in the reperfusion phase is usually self-limiting and resolves spontaneously. Resolution of hyperfibinolysis is an early indicator of graft function. In the absence of profuse bleeding, prophylactic use of hemostatic products prior to invasive procedures and liver transplantation is not recommended.

Dynamic, whole blood point of care viscoelastic hemostatic tests [VHT] such as Thromboelastography [TEG®] and rotational thromboelastometry [ROTEM®] indicates the status of clot formation, clot strength and fibrinolysis within a short turnaround time. VHT guided hemostatic therapy does not increase the risk bleeding or thrombotic complications [19].

VHTs reliably predict bleeding and need for blood products in LT resulting in reduced usage of blood products, a lower rate of complications and improved survival after LT[19].

ROTEM, EXTEM MCF correlates with platelet count and fibrinogen levels. EXTEM A5, an early indicator of impaired clot firmness secondary to critically low levels of platelets and fibrinogen levels, is a good linear predictor of EXTEM MCF. FIBTEM MCF which correlates with fibrinogen levels is used to differentiate low platelet count from a low fibrinogen level, as the cause of impaired clot firmness [20, 21].

The lack of facilities for Point-of-care VHT testing within the operation theatre complex at CNCLD limits its usefulness in managing rapidly evolving coagulopathy.

8. Transfusion of blood products

Advances in surgery, anaesthesia and VHT guided coagulation therapy have revolutionized management of bleeding in liver transplantation. Increased requirement for blood products could reflect coagulopathy and severity of underlying ESLD. VHT guided management of coagulation reduces the risks of fluid overload, raised pulmonary arterial and portal venous pressure and adverse effects attributed to blood products [22-24]

The use of FFP in LT needs to be considered carefully due to concerns regarding its safety, and lack of evidence of benefit particularly when used to in the setting of impaired thrombin generation [19, 25]. The number of units of packed red cells and the volume of plasma transfused correlates with reduced one year survival following liver transplant [22, 26]. Transfusion related immune modulation and risk of infection, neutrophil-mediated exaggerated inflammatory response to tissue damage and ischemia-reperfusion adversely impact outcome following LT. Red cell transfusion is an independent risk factor for early acute kidney injury post liver transplant [27]. Platelet transfusion is a risk factor for acute lung injury, graft injury and correlates strongly with poor post-transplant outcome [22, 28-30].

Advances in perioperative care, evidence linking blood products with adverse outcomes, use of protocols based on VHT and the availability of factor concentrates have led to a reduction in transfusion requirements [19, 31]. At CNCLD, management of coagulopathy in LT is based on the Essen university A5 protocol [19]. The use of platelet concentrates and fresh frozen plasma is restricted to patients with significant bleeding and is guided by VHT. Cryoprecipitate use as the source of fibrinogen is guided by VHT, in the presence of clinically significant bleeding. The use of factor concentrates is limited due to high cost. Leukocyte depleted red blood cell transfusion is based on need.

9. Enhanced recovery after liver transplant surgery

Adoption of a protocol of evidence-based interventions including the use of advanced hemodynamic monitoring, adherence to a restrictive fluid protocol, viscoelastic test guided use of blood products and monitoring the depth of anaesthesia has resulted in improved outcome following LT.

Adoption of such a protocol is associated with early extubation, early mobilization, reduction of postoperative ventilation, postoperative complications, length of intensive care and hospital stay and cost. Adoption of the protocol has been linked to a rapid pace of recovery even in the sicker, high MELD patients [32-34].

Achievement of enhanced recovery following LT is a surrogate marker of the quality of perioperative care. Since adoption of this strategy, 20% of patients undergoing LT at CNCLD have been extubated in operation theatre and fast tracked to discharge.

10. Summary

Haemodynamic management in liver transplantation for cirrhosis is challenging due to a complex interplay of factors associated with ESLD, liver graft, surgery and anaesthesia. As complex changes in haemodynamics and coagulation in this setting are better understood adoption of evidence based haemodynamic management, haemostatic interventions guided by viscoelastic hemostatic interventions in combination with an enhanced recovery protocol have resulted in improved outcomes following liver transplantation.

All authors disclose no conflict of interest. The study was conducted in accordance with the ethical standards of the relevant institutional or national ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

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Annexure 1

Guidance for Haemodynamic Management in Liver Transplantation at the Colombo North Center for Liver Disease (CNCLD)

Preoperative assessment and optimization

- Detailed clinical assessment (ABG if SpO2 less than 93%)
- Screening test – Six-minute walk distance more than 250m
- Echocardiography – Ejection fraction more than 50% and mean pulmonary arterial pressure below 40mmHg
- Dobutamine stress test, exercise testing, serum creatinine prior to coronary angiogram following multidisciplinary consensus
- Nutritional assessment and optimization
- Graded exercise regime, incentive spirometry
- Counselling

Intraoperative management

- Pre induction ECG, NIBP, SpO_2, forced air warmers
- Femoral and radial intra-arterial blood pressure. Nasopharyngeal thermometer
- Right internal jugular vein: a) Central venous catheter, b) haemodialysis catheter coupled to Belmont© rapid infuser
- 'Flowtrac' / 'LiDCO' connected to femoral artery and Oesophageal doppler
- MAP +/- 20% pre-induction pressure
- Cardiac index 2.5-3.5L/kg/m^2
- Stroke volume variation less than 12-15%
- Contractility – Peak velocity (PVel) >65 cm/s
- Systemic vascular resistance index 1500 – 2400 dynes/s/cm^5/m^2
- Central venous pressure < 5 mmHg, Central venous oxygen saturation 60-70% and serum lactate
  Rotational thromboelastometry: Hemostatic therapy of bleeding guided by ROTEM: *based on clinical assessment in combination with Essen University A5 protocol*)
  Sampling for ROTEM: Base line, 15 minutes prior to anhepatic phase, 15 minutes after caval clamp, 15 minutes prior to reperfusion, 15 minutes, and 45 minutes after reperfusion and 15 prior to extubation or transfer to intensive care unit, 15 min following hemostatic intervention
- Hemoglobin 7-9g/dl
- Urine output 0.5ml/kg/hour
- IV fluid: Compound sodium lactate / 5% albumin (0.9% saline if Na+ <130meq/l)
- Noradrenaline, dobutamine, vasopressin (Up to 4.8u/hr), calcium gluconate infusions to achieve above targets.
- Vasoplegic syndrome (SVRI < 800 & CI > 5 despite vasopressin 2u/hour and noradrenaline 1micg/kg/hr) – Methylene blue (1-2mg/kg over 10-15 minutes, 2mg/kg/hour infusion), hydroxocobalamin (125-250mg bolus / 250-500mg/hr infusion: Max 5g), Intravenous enriched immunoglobulins
- Coordinate with surgeon to control application and release of vascular clamps
- Boluses of 1:200,000 adrenaline, calcium gluconate during reperfusion
- Consider fast tracking if alert, intact gag reflex, respiratory rate 12-18/minute, normothermic, normal blood gas, no excessive bleeding, nearly normal ROTEM, single vasopressor, noradrenaline dose less than 0.1micg.kg/min, UOP> 0.5ml/kg/hr

Courtesy: Bhagya Gunetilleke, Colombo North Center for Liver Disease, Faculty of Medicine, University of Kelaniya, Sri Lanka