

A Quest for Enhanced Recovery After Liver Transplant at The Colombo North Center for Liver Disease: The First Decade

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Cirrhosis is a significant contributor to non-communicable disease related deaths in Sri Lanka and the only cure for cirrhosis constitutes liver transplant. Nonalcoholic fatty liver disease (NAFLD) which is the hepatic component of the metabolic syndrome is the main aetiology of cirrhosis in patients presenting for liver transplant at CNCLD. Enhanced recovery after surgery (ERAS) is a concept originally adopted in colorectal surgery, and is a multimodal- multidisciplinary approach to perioperative care aiming to reduce perioperative surgical stress response and improve short-term outcome. Targeting improved outcome, components of ERAS have been incorporated in the perioperative care of liver transplant at the Colombo North Center for Liver Disease since 2016. Sri Lanka needs to define its own enhanced recovery after liver transplant (ERALT) protocols based on local data and audit performance.

Keywords: Enhanced recovery after surgery (ERAS), liver transplant

Chronic liver disease is a significant health care issue in Sri Lanka. In fact, cirrhosis is the 9th highest contributor to Non communicable disease (NCD) related death in Sri Lanka¹

Importantly, the three main causes of NCD related deaths in Sri Lanka, ischaemic heart disease, stroke and diabetes mellitus, are associated with metabolic syndrome¹. The prevalence and burden of non-alcoholic fatty liver disease (NAFLD), has long been considered the hepatic component of metabolic syndrome, which is most likely overshadowed by other clinical manifestations and consequently under

estimated. Unsurprisingly, NAFLD is the main aetiology of cirrhosis in patients presenting for liver transplant at the Colombo North Center for Liver Disease (CNCLD)².

NAFLD is a spectrum of chronic liver disease, extending from potentially reversible nonalcoholic fatty liver (NAFL) to the irreversible stages of cirrhosis. Approximately, 10% with NAFL progress to cirrhosis. Asians are genetically predisposed to NAFL due to the presence of a variant of the PNPLA3 gene³.

Though global prevalence of NAFLD was estimated at 20–25% its prevalence in an adult urban Sri Lankan population was 33%. Significantly the prevalence of NAFLD in urban adolescents was as high as 8.4%^{3,4}.

The ‘Ragama health study’ conducted in an urban population in Sri Lanka, revealed an increase in the prevalence of metabolic syndrome from 39% in 2007 to 47% within a period of 7 years. Considering the prevalence of metabolic syndrome, its association with NAFLD and its effect on a most productive segment of the

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population, the potential demand on health care resources in the future is most likely underestimated⁵.

The natural course of cirrhosis is characterized by progressive deterioration of liver function punctuated by episodes of acutely chronic liver failure. Liver transplant offers the only cure for cirrhosis which would otherwise lead to decompensation, multiple organ failure or hepatocellular carcinoma (HCC) and finally death^{6,7}.

The experience gained from over 200 laboratory experiments and the use of multi drug immune suppression therapy in renal transplant has enabled a team led by Thomas Starzl (Surgeon) and Tony Aldrete (Anaesthetist) to carry out the first liver transplant in 1963^{9,10}.

Uncontrolled coagulopathy and bleeding that resulted in the intraoperative death of the recipient child. The four subsequent liver transplants were also unsuccessful with patients succumbing to bleeding or thrombosis. Thus, the team decided to halt Liver transplants^{8,9,10}.

My association with liver (liver disease, liver transplant?) commenced in 2010 as a member of the team, which carried out the first successful liver transplant in Sri Lanka in 2010¹¹. The team from CNCLD which commenced liver transplant in 2011, carried out the first successful transfusion free liver transplant with fast track extubation in Sri Lanka in 2018 and first ABO incompatible liver transplant in 2022^{11,12}.

The gross demand supply mismatch remains a problem in Sri Lanka as it does globally. The absence of an efficient system to identify potential donors, the lack of an equitable, need based system of organ allocation, migration of trained personnel and the shortage of infrastructure limits the number of liver transplants. The poor quality of donor graft is a unique problem, which compounds the donor organ shortage¹³. A multitude of factors including disease severity, comorbidity, and

quality of the graft, perioperative management and infrastructure affect recovery and the ultimate outcome.

After the initial success, infection, bleeding and graft failure began to take its toll and in 2014, the team took the difficult decision to halt Liver transplant at CNCLD.

Enhanced recovery after surgery (ERAS) is a multimodal- multidisciplinary approach to perioperative care. It aims to reduce perioperative surgical stress response and improve short-term outcomes by reducing complications, shortening length of ICU and hospital stay.

Enhanced recovery after surgery (ERAS) a concept well established in colorectal and other fields of surgery is gaining traction in the field of liver transplant.

The wide spectrum of aetiology, comorbidity, extreme deranged physiology, the complexity of treatment and perioperative care and the relatively small number of transplants carried out may have contributed to the delay in development of evidence-based ERAS guidance for liver transplant^{14,15,16,17}.

The focus of the oration was the adaptations to perioperative anaesthetic management in relation to frailty, haemodynamics, blood products and extubation at CNCLD in a quest for enhanced recovery since liver transplants were re-started in 2016.

These practices were initially incorporated in the perioperative care pathway of liver resection and subsequently adopted in liver transplant.

At CNCLD, the enhanced recovery after liver transplant (ERALT) care pathway begins with the referral to the multi-disciplinary clinic at the Faculty of Medicine, University of Kelaniya.

A typical patient with CLCD would be malnourished, sarcopenic with low-grade encephalopathy, often depressed with reduced

cardiovascular, respiratory, coagulation and renal reserves. Diabetes mellitus and portal hypertension. Patients with cirrhosis awaiting liver transplant are physically deconditioned with low functional capacity. These contribute to poor short-term outcome, excessive use of health-care resources and a poor quality of life, both before and after liver transplantation.

The patients undergo a comprehensive preoperative anaesthetic screening including assessment of the Liver frailty index, 6 minute walk test and pulse oximetry. Selected patients undergo further assessment including cardiopulmonary testing¹⁸.

Frailty a multi-dimensional concept is defined as decreased physiologic reserves and vulnerability to health stressors predisposing to adverse health outcomes. It is associated with malnutrition, sarcopenia, progressive immobility and decreased energy expenditure and is a critical determinant of the wait list, ICU and post-transplant mortality, length of stay in hospital and cost of health care¹⁹.

Frailty is one of many criteria used to evaluate transplant candidacy and suitability¹⁹.

Prehabilitation is key to minimizing the adverse impact of frailty on outcome. A prehabilitated patient is more likely; despite postoperative complications to recover and be independent^{20, 21}

All patients attending the clinic are provided advice on nutrition and exercise.

In our cohort of patients, the mean liver-specific frailty index (LFI) was 4.13(SD-0.49). Only 20% could be categorized as robust.

On follow up, only 12% had complied with the prescribed home based exercise regime. The main reason for the failure to comply was tiredness²¹.

The Model for End stage Liver Disease Na(MELDNa) is used as a predictor of risk of death while awaiting a liver transplant and is

used to prioritize patients based on the 'sickest first' policy.

A study of our cohort indicated that preoperative MELDNa is as good a predictor of postop mortality as postoperative APACHE II. Therefore, preoperative MELDNa has a potential for use as a prognostic marker compared to APACHE II²².

Hemodynamic instability (HDI) during LT is multifactorial, is extremely common and is linked to poor graft function and outcome. Sudden severe haemodynamic fluctuations induced by surgical manipulation is complicated by the presence of coagulopathy, portal hypertension, splanchnic vasodilation, cirrhotic cardiomyopathy and systemic vasoplegia. Poor graft quality worsens instability.

Despite intense investigation, an optimal haemodynamic management strategy remains elusive^{18,23}

On average, liver transplant recipients suffer from more than three early postoperative complications; renal, pulmonary, and infectious being the most common. Perioperative variables, including hemodynamic variations and transfused volume, have been associated with these complications²⁴. The ultimate haemodynamic goal is to find the sweet spot required to maintain optimal blood flow and oxygen delivery to tissues²⁴. The sweet spot varies between patients as well as within the same patient. A goal directed restrictive fluid strategy aims to hit the sweet spot using the minimum volume of intravenous fluids guided by clinical and haemodynamic parameters. We use a combination of parameters including dynamic measures of fluid responsiveness to achieve our goals. The mainstays of haemodynamic monitoring in the pre-2016 era consisted of arterial and central venous pressure. Oesophageal Doppler and pulse contour derived cardiac output monitors both with well-known limitations in the setting of liver transplant have been the mainstay since post 2016.

Transoesophageal echo and pulmonary artery catheters were not available in the unit.

A Goal-directed haemodynamic strategy tailored to the various surgical phases is more effective than a fixed fluid management strategy²³.

Intraoperative restrictive fluid management strategies have protective effects in the setting of liver transplant. These include reduced blood loss and pulmonary complications; a shorter duration of post op ventilation and ICU stay.

Increased Central venous pressure secondary to liberal use of intravenous fluid correlates with raised portal venous pressure and bleeding. Clinical equipoise still remains the best fluid management strategy to adopt for this population^{23,24}.

A restrictive fluid strategy invariably requires the use of vasopressors and inotropes; both with well-known adverse effects. Evidence indicates that the incidence of AKI in liver transplant is not increased by the adoption of a restrictive fluid strategy²⁴.

Following the adoption of a Goal directed haemodynamic strategy with restrictive use of fluids, the mean intraoperative intravenous fluid volume has remained approximately 3000ml.

Intravenous fluids are infused via the rapid infuser warmer, which permits accurate tracking of infused volume while minimizing hypothermia¹³.

In end stage liver disease (ESLD), coagulation is rebalanced with reduced reserves. Disruption of this precarious balance by stressors such as surgery and sepsis surgical may result in hemorrhage or thrombosis²⁵.

In ESLD, Conventional tests of coagulation such as platelet count and prothrombin time, tend to overestimate the bleeding risk.

The use of a rotational thromboelastometry based algorithm reduces blood products usage without

a parallel increase in bleeding or thrombotic complications. Following the adoption of the Essen University A5 algorithm at CNCLD in 2016, the use of fresh frozen plasma and platelet concentrate declined drastically. Fibrinogen deficiency; the commonest haemostatic abnormality encountered, is treated with cryoprecipitate^{13,25,26}.

Rotational thromboelastometry is used to guide blood product use prior invasive procedure in cirrhotics at CNCLD.

In 99 cirrhotics including 27% who were Childs B or C, who underwent ultrasound guided microwave ablation of hepatoma, none were transfused with blood products in the peri-procedure period.

Red cell transfusion is associated with a dose related correlation with Acute kidney injury and reduced one year survival²⁵. A restrictive red cell transfusion policy with a transfusion threshold of 7-9g/dl has been adopted at CNCLD.

Defined as tracheal extubation within 3 hours of completion of surgery, early extubation positively impacts on recovery and is a key performance indicator.

The first transfusion free liver transplant and on-table extubation was carried out in 2017 without complications²⁷.

Early extubation after liver transplant disproved the belief that a period of postoperative mechanical ventilation was essential to ensure safe recovery²⁸.

The quality of the donor liver in terms of steatosis impacts on outcome.

Graft steatosis increases the severity of the ischemia reperfusion injury, primary non-function and biliary complication. Graft steatosis exceeding 30% is common in our donors.

A study of 34 potential live donors revealed a rejection rate of 85% with nearly half

demonstrating to have Non-alcoholic fatty liver disease²⁹.

The post liver transplant 1 year survival improved from 30.7% in the pre 2014 epoch to 60.7%, post 2016.

An important goal of liver transplant is to return the patient to health and not just treat disease.

Preoccupation with cost and mortality metrics to the exclusion of overall health and quality of life does not meet the goals of liver transplant.

Enhanced recovery protocols are an essential component of a multipronged strategy to achieve a good outcome following liver transplant³⁰.

Importing practices without adapting to local requirements and the absence of continuous quality improvement leads to suboptimal outcomes. We in Sri Lanka need to define our own ERALT protocols based on local data and audit our performance.

Summary

Sri Lanka is facing a rapid rise in the prevalence of metabolic syndrome and its hepatic component - nonalcoholic fatty liver disease (NAFLD). Approximately 10% of patients with NAFL progress to cirrhosis. The only cure for cirrhosis is liver transplant. The concept of Enhanced recovery after surgery (ERAS) encompasses multiple evidence-based perioperative interventions aimed at improving short-term outcome.

Conflicts of Interest

The author has no conflicts of interest to declare.

Financial disclosure

None

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