

The journey of liver transplantation: Milestones covered and the road ahead

Liver transplantation has now become an established approach for managing end-stage liver diseases, and the journey in the complex procedure of liver transplantation has come a long way, witnessing many ups and downs. Better understanding of the physiological and pathological changes in the context of end-stage liver disease has made anesthesia, an important denominator for the successful outcome of this complex surgical procedure.

As the prevalence of the liver disease is rising, especially with hepatitis C infection, alcoholic/nonalcoholic-related liver disease, and hepatocellular carcinoma in an aging population, there is a significant impact on the perioperative and intensive care services. Perioperative mortality during liver transplantation is of concern, and it increases in proportion to disease severity but is affected by functional status, nutritional impairment, other comorbidities, and requirement for organ support. Model for End-stage Liver Disease (MELD) score is now commonly used to allocate and prioritize patients for transplant and has gained more importance than the conventional Child-Pugh scoring.^[1] MELD score uses patient's serum bilirubin, prothrombin time, and creatinine to predict survival based on a calculation. Serum sodium concentration has been incorporated in the UK model of MELD to make it more meaningful.^[2,3]

Long standing liver disease results in high flow state and shunting between pulmonary, peripheral, and splanchnic beds, resulting in increase of cardiac output. This causes imbalance in splanchnic and peripheral compartments, causing several significant effects which need to be addressed.^[4] Among the various issues of concern for the anesthesiologist, the most significant are portal hypertension, contracted central blood volume, and cardiac changes which are specific to liver disease.

Portal hypertension a result of increased splanchnic flow rather than of intrahepatic resistance contributes to ascites, bacterial translocation, and aggravated bleeding during surgical dissection. The contracted central blood volume stimulates a powerful neuroendocrine response mimicking volume depletion, causing prerenal failure, or hepatorenal syndrome making these patients more susceptible to perioperative renal injury.^[5]

The issue of fluid balance in patients of advanced liver disease undergoing liver transplantation or any other surgery is a tight rope walk and caution is to be exercised while administering fluids as it can increase portal hypertension. This especially makes bleeding, more worse, in procedures involving division of portosystemic collaterals.^[6]

The anesthesiologist should be aware of the cardiac changes due to high flow state in this condition, resulting in cirrhotic cardiomyopathy. This causes impaired responsiveness to preload, afterload, QT prolongation, and increased chamber dimensions.^[7] The diastolic dysfunction associated with raised cardiac output can precipitate secondary pulmonary hypertension or portopulmonary hypertension.^[8]

Evidence suggests that these liver-related changes have important therapeutic implications in use of vasopressors, especially in the setting of hepatorenal syndrome. Vasopressin usage during the peritoneal dissection phase of liver transplantation has shown to reduce portal flow and pressure,^[9] and phenylephrine helps to maintain the reduction in portal pressure while increasing central venous and mean arterial pressures. These measures aid in renal function maintenance and minimize surgical bleeding. This helps in maintaining renal function and reduces operative bleeding due to volume shift from splanchnic to central venous compartment.^[10] Vasopressor therapy in low dose, especially in an underlying liver disease undergoing general anesthesia, maintains adequate cardiac output, with relatively less input of volume. It also ensures adequacy of renal and splanchnic blood flow. This prevents disruption of vascular intimal glycocalyx, which is the causative factor for fluid translocation and edema at capillary level.^[11] This issue is to be borne in mind while dealing with any patient of liver disease subjected for surgery.

Pulmonary hypertension associated with advanced liver disease has to be evaluated with transthoracic echocardiography as it is a treatable entity. The possible predisposition to renal function compromise and sepsis should be borne in mind and fluid administration adjusted. Hypotension with general anesthesia requires management with a low vasopressor and be guarded fluid administration dose.

Advances in the understanding of the coagulation system in liver disease in the form of reduced Vitamin K-dependent factors, protein C, and antithrombin III have also had a significant clinical impact. Routine tests of prothrombin time and activated partial thromboplastin time are often misleading in predicting bleeding in liver transplantation.^[12] Similarly, although platelet numbers and *in vitro* function may be reduced, more than

adequate levels of factor VIII and Willebrand factor, typically seen in cirrhosis, may compensate.^[13] The fibrinolytic system is also affected causing fibrinolysis on a lower grade. This can be aggravated especially during transplantation and can be managed with prophylactic tranexamic administration.^[14] The routine clinical practice of administering fresh frozen plasma is questionable and now stands disputed. The management is best based on clinical findings such as leaky surgical field or failure of blood to clot. Clinical coagulopathy if present due to low fibrinogen can be effectively managed with prompt replacement.^[13,14] Thromboelastography (TEG) has been an important tool helping to identify multifactorial coagulation impairment and aids in institution of proper blood component before loss of valuable time. This aid has now been accepted as a point of care requirement in transplantation procedures.^[15]

Another challenging situation is the issue of significant hyponatremia, common in severe liver disease and liver transplantation. This has also given us insight into the risks associated with rapid correction of hyponatremia. Myelinolysis is a major concern and a hazard if serum sodium concentration rises abruptly, especially when citrated blood products are administered in large quantity. A safe and manageable threshold value for elective surgery is probably 125 mmol/l.^[16] A postoperative fall in serum sodium concentration is associated with a significant increase in hospital morbidity and mortality. Vigilance is essential in monitoring of serum sodium and potassium concentration in the postoperative period, especially for hyperkalemia when large quantity of bank blood is used.

Routine use of preoperative echocardiography and TEG is beneficial especially for major elective liver surgeries. Early use of alpha-agonists for anesthesia-induced hypotension, avoiding overzealous administration of fluids, will preserve coagulation and renal function and minimize portal hypertension. Tranexamic acid is safe when bleeding is anticipated or uncontrolled. The use of factor concentrates is to be considered whenever significant coagulopathy so dictates. Postoperatively, it is mandatory that all patients with high MELD scores be managed in intensive care with special attention to mental alertness, sodium balance, and urine output.

The issue of meeting the imbalance between demand and supply in the field of liver transplantation still needs to be addressed. The gulf between both is only increasing in spite of institution of best practices and policies in tackling this rather complicated issue. There has been a significant improvement in the techniques making the availability of donor liver more in the form of utilizing marginal liver, reduced size liver transplantation, liver reduction, split liver transplantation, living-related transplantation – especially in the Asian

continent and usage of nonheart-beating donors, auxiliary liver transplantation – for fulminant failures and metabolic disease. The idea of xenotransplantation though found to be very optimistic initially is unlikely to be a good substitute for human liver in clinical transplantation at least without major genetic engineering.

The road ahead: Liver transplantation has become a victim of its own success, with the inexorable rise in patients waiting for surgery and a donor pool who remain static. The future must involve improved utilization of potential organ donors and their optimization. Living donor transplantation has become today a viable option to redress the shortage of donors. Improvements in immunosuppression have had a major effect on the survival of liver transplant patients, a phenomenon that is promising. The journey of liver transplantation initially had been rough and bumpy, but with the experience gained, better understanding of the physiopathological changes, improved surgical techniques, better postoperative care, and better immunosuppression, the road ahead now seems to be smooth and clear.

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