

What every pediatrician should know about liver transplantation

Maria Ajdari: Department of Surgery, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Reza F. Saidi: (*Corresponding author), Department of Surgery Shariati Hospital, Digestive Disease Research Institute Tehran University of Medical Sciences, Tehran, Iran. rfsaidi@hotmail.com

Received: 9 Jan 2017

Accepted: 29 June 2017

Abstract

Liver transplantation is the treatment of choice for children with end-stage liver disease. Improvement in outcomes (allograft and patient survival) has led to widespread use of pediatric LT worldwide. This success is due to improvement in patient selection, transplant surgery, anesthesia/postoperative care and immunosuppression management. This review will focus on different aspects of LT which every pediatrician should know to provide better patient care.

Keywords: Liver transplantation, Transplant surgery, Children

Background

Liver transplantation (LT) is a lifesaving procedure and the treatment of choice for kids suffering from end-stage liver disease (ESLD). The first successful LT was done 1967 at Denver US. The first pediatric LT in Iran was performed at Shiraz University (1). This review will discuss different aspects of pediatric LT which every pediatrician should be known.

Chronic Liver Disease and Indications Pediatric LT

Chronic liver disease in children which requires LT can be divided into 4 categories:

- 1- Progressive chronic liver diseases which can progress to ESLD such as chronic viral hepatitis (B or C), acute liver failure or biliary atresia (2-4).
- 2- Nonprogressive chronic liver disease: This disease do not progress to ESRD. However, they can cause impaired child's growth and well-being due to severe itching failure to thrive or malabsorption. Alagille syndrome or cholestatic liver disease are in this category (3, 5).
- 3- Metabolic diseases such urea cycle defects, glycogen storage diseases, tyrosinemia, Crigler-Najjar syndrome familiar hypercholesterolemia or hyperoxaluria (3).
- 4- Secondary liver disease such as cystic fibrosis or secondary biliary cirrhosis due to stone (6).
- 5- Primary liver tumors such as hepatolastoma

(7).

These kids considered for LT after extensive multidisciplinary workup. Lack of patient and family compliance, poor psychological support, advanced cardiovascular or pulmonary diseases, uncontrolled sepsis, irreversible multiple organ failure, AIDS, and active cancer (except selected case of HCC) are contraindications for LT. ESLD can manifest as bleeding from esophageal varices, intractable ascites, hepatic encephalopathy, or hepatorenal syndrome (8-10).

Sources of Liver Allografts

The majority of livers are procured from brain death donors. Nevertheless, the increasing number of patients dying on the waiting list due to the shortage of livers has prompted the transplant community to use more organ resources. Their effort to expand the donor pool has provided alternative ways of organ supply, including using live donors or split-LT. The ideal donor criteria include young donor died after trauma.

Living-donor liver transplantation (LDLT) is an established treatment for ESLD. In Asian countries, approximately 90% of donor organs for LT are obtained from live donors, as the deceased donor rate is low due to social and religious factors. LDLT has several well-documented advantages, including the use of a graft from a healthy donor with short ischemic time, the ability to schedule surgery electively, a reduced risk of the recipient dying on the waiting list, and it al-

lows for the recipient to be medically stabilized. Disadvantages of LDLT are the higher rate of surgical complications for both the donor and recipient and a potential risk of small-for-size syndrome. LDLT carries inherent risks for the healthy donor. Therefore, careful selection of the donor and recipient is crucial to minimize risks and complications, and to obtain an acceptable outcome. Initially donors undergo psychosocial evaluation to assure there is no coercion. Next, donors are evaluated by clinical examination and serologic testing for liver disease, renal disease, and viral hepatitis. Diagnostic studies to evaluate the vascular and biliary anatomy of the liver are done next. Several options for preoperative imaging are available which include non-invasive modalities such as multi-phase liver computed tomography, duplex ultrasonography, and magnetic resonance imaging. The risk of donor death after partial liver donation has been reported 1/500 worldwide. The complication death is about 30% (bleeding, bile leak, thromboembolic event or incisional hernia) which depends on the experience of the LT team. Left lateral sector (segments 2 and 3) or monosegment can be used in children depended on the kid's size.

Liver Allocation

Priority of organ allocation should be based on equity and justice to use valuable organ resources. LT is a lifesaving procedure. In US, liver allocation is based on patients' risk of dying while waiting on the list for LT. This risk is calculated based on PELD (pediatric end-stage liver disease) score. PELD score is a logarithmic based on patient's age, bilirubin, albumin and INR. MELD score can predict chance of dying within 90 days without LT. By switching to PELD for liver allocation, wait list mortality has decreased in US without change in post-LT survival. However, PELD score has its own limitation. Some patient's disease severity also is not represented by PELD such as metabolic disorders (12). These patients have to PELD exception to compete with other ESLD kids for LT. Patients with acute live failure should be transplanted as soon as possible regardless of PELD score (8).

Transplant Surgery

LT surgery have three phases:

- 1- Hepatectomy phase: LT is done orthotopically. During this step, the whole liver has to be removed. Due to portal hypertension, this phase can be associate with bleeding. Meticulous dissection and a good anesthesia team is crucial for

the management of this step.

- 2- Anhepatic phase: during this step, the new allograft is brought out of the cold storage and anastomosed to the patient's circulation system. The new liver is getting warm at this moment and this phase should be completed within 30-40 minutes (warm ischemic time). During this phase, the IVC or hepatic veins anastomosed are done first. Recipient's IVC can replaced by donor IVC (classic technique), or donor suprahepatic IVC is sewn to the cuff of hepatic veins and donor infrahepatic IVC is ligated (piggy-back technique). Next, portal vein anastomosis is done in end-to-end fashion next.
- 3- Reperfusion phase: The clamps will be released and liver will be reperfused. Hepatic artery and bile duct anastomosed are done in end to end fashion. As all toxins from liver and gut can be released to systemic circulation after reperfusion (ischemia reperfusion injury), this phase can also be associated with hemodynamic instability which requires an experience anesthesia team to manage the situation.

Postoperative Care and Immunosuppression

Patient will be transfer to PICU for monitoring postoperatively. Liver allograft will be monitored clinically and base on laboratory tests. If the liver allograft functions properly, patient would gain consciousness, with hemodynamic stability and without coagulopathy. The liver function test should gradually normalize. Doppler ultrasound should be done routinely to access blood flow.

Immunosuppression (IS) regimen should start immediately. Immunosuppressive therapy includes induction and maintenance therapy. The induction agents are added to the standard immunosuppressive agents to prevent or reduce the incidence of early rejection rates following LT. Induction therapy consists of anti-CD25-receptor antibodies (basiliximab, daclizumab), an anti-CD52 monoclonal antibody (alemtuzumab), or depleting polyclonal antibodies (thymoglobulin or ATG). The standard immunosuppressive regimen is a triple therapy regimen that consists of calcineurin inhibitors (CNI; cyclosporine or tacrolimus), steroids, and MMF. CNIs are the cornerstone of the immunosuppressive regimen at most liver transplant centers. Nevertheless, therapy with CNIs is associated with adverse effects such as nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, and hyperlipidemia. Corticosteroids usually have the dose-dependent side effects that include osteoporosis, diabetes, Cushing syndrome, hypertension, and hyperlipidemia. MMF

can cause bone marrow or gut toxicity (13, 14)

Complications

Early complications of LT are primary non-function (PNF), vascular compromise (hepatic artery or portal vein thrombosis), infectious issues (such as line infection, pneumonia, urinary tract infection or intraabdominal abscesses) or bile leak (15).

PNF usually occurs in 4-6% of cases and presented with encephalopathy and coagulopathy. The only treatment is immediate re-transplantation. Early hepatic artery thrombosis (within 2 weeks postoperatively) also requires re-transplantation due to high relate of sepsis from biliary complications. Portal vein thrombosis can be managed with re-operation and thrombectomy.

Late complications are biliary strictures, vascular compromise (thrombosis or stricture), opportunistic infections (viral or fungal), metabolic syndrome, IS side effects and malignancies (skin cancer, lymphoma).

Late hepatic artery thrombosis can be asymptomatic or present itself with biliary complications such as biloma or strictures. Fortunately most of these complications can be managed by interventional radiology or endoscopic approach. Re-transplantation is rarely required. Late vascular complication requires vascular endovascular intervention.

Follow-up

Initial follow-ups include blood tests and duplex ultrasound of the transplanted organ to monitor for patency of vasculature, rejection and infection. If rejection is suspected, a liver biopsy should be performed. LT recipients are at higher risk than the general population for malignancy due to IS. The most common neoplasms are skin cancer and post-transplant lymphoproliferative disease (PTLD). Cardiovascular, infectious, malignancy are the most common causes of patient death over the long term. Patients should be monitored and treated for metabolic syndrome, DM, hyperlipidemia and osteoporosis. Patients should also followed regarding recurrence of primary disease (hepatitis) in the allograft. Treatment should be started soon. Fortunately, the risk of allograft failure and need for re-transplantation is low.

Outcome

Several factors are predictors of post-transplant outcomes following LT. These factors can divided or donor-, recipient- and operative- related param-

eters. Donor parameters which are predictor of outcome are: advanced age, high BMI, cause of brain death (stroke vs trauma), length of hospitalization, and use of pressers, liver function, sodium level, reduced/split grafts vs whole graft, steatosis, and cold ischemia time. The recipient parameters include urgent status, renal dysfunction, age, ventilation requirement, and HCV. Operative factors are the amount of blood loss and blood product administration, the lack of immediate bile production, low urine output, CIT > 12 hr. and warm ischemia time > 45 min. Finally, postoperative indicators are parameters such as elevated ALT and AST, serum bilirubin, serum creatinine, and prothrombin time. Liver transplant survival has increased over the past decade. One- year allograft and patients survival are approximately 85% and 90% respectively. Five- year allograft and patients survival are approximately 75% and 80% respectively. (8-11).

Conflicts of interest: None declared.

References

1. Malek-hosseini SA, Salahi H, Lahsaei M, et al. Initial experience with liver transplantation in Iran. *Transplant Proc.* 2013;35:375-6.
2. Govindarajan KK. Biliary atresia: Where do we stand now? *World J Hepatol.* 2016 Dec 28;8(36):1593-1601.
3. Stefan Farkas, Christina Hackl, and Hans Jürgen Schlitt. Overview of the Indications and Contraindications for Liver Transplantation. *Cold Spring Harb Perspect Med.* 2014 May; 4(5): 123-8
4. Halliday N, Westbrook RH. Liver transplantation: need, indications, patient selection and pre-transplant care. *Br J Hosp Med (Lond).* 2017 May 2;78(5):252-259
5. Tomáš Dědič, Milan Jirsa, Radan Keil, Michal Rygl, Jiri Šnajdauf, and Radana Kotalová1, Alagille Syndrome Mimicking Biliary Atresia in Early Infancy. *published online 2015 Nov 30.*
6. Melzi ML, Kelly DA, Colombo C, Jara P, Manzañares J, Colledan M, Strazzabosco M, DeLorenzo P, Valsecchi MG, Adam R, Gridelli B, Assael BM; EGSLTCF; European Liver Transplant Association (ELTA); European Cystic Fibrosis Society (ECFS). Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. *Transpl Int.* 2006 Sep;19(9):726-31.
7. Trobaugh-Lotrario AD, Meyers RL, Tiao GM, Feusner JH. Pediatric liver transplantation for hepatoblastoma. *Transl Gastroenterol Hepatol.* 2016 May 20;1:44.
8. Saidi RF. Current Status of Liver Transplantation. *Arch Iran Med.* 2012 Dec;15(12):772-6

9. Kohli R, Cortes M, Heaton ND, Dhawan A. Liver transplantation in children: state of the art and future perspectives. *Arch Dis Child*. 2017 Sep 16.
10. Rawal N, Yazigi N. Pediatric Liver Transplantation. *Pediatr Clin North Am*. 2017 Jun;64(3):677-684.
11. Parmar A, Vandriel SM, Ng VL. Health-related quality of life after pediatric liver transplantation: A systematic review. *Liver Transpl*. 2017 Mar;23(3):361-374.
12. Capone K, Amirikian K, Azzam RK. Pediatric Liver Transplantation: An Update for the Pediatrician. *Pediatr Ann*. 2016 Dec 1;45(12):e439-e44
13. I Miloh T, Barton A, Wheeler J, Pham Y, Hewitt W, Keegan T, Sanchez C, Bulut P, Goss J. Immunosuppression in pediatric liver transplant recipients: Unique aspects. *Liver Transpl*. 2017 Feb;23(2):244-256
14. Tsampalieros A, Knoll GA, Molnar AO, Fergusson N, Fergusson DA. Corticosteroid Use and Growth After Pediatric Solid Organ Transplantation: A Systematic Review and Meta-Analysis. *Transplantation*. 2017 Apr;101(4):694-703.
15. Youssef D, Niazi A, Alkhouri N. Long Term Complications in Pediatric Liver Transplant Recipients: What Every Pediatrician Should Know. *Curr Pediatr Rev*. 2016;12(3):209-221.