Theme Symposium

LIVER TRANSPLANTATION

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Liver transplantation (LT) in children is now established therapy for acute and chronic liver failure. The formulation and acceptance of brain death criteria, establishment of dedicated transplant centres, the refinement in surgical techniques, improvement in anesthesia, perioperative care and access to newer immunosupressant drugs have now resulted in significant improvement in outcome.

THE first milestone in the field of management of end stage liver disease (ESLD) was laid with the attempt of a human liver transplantation (LT) of a 3-year-old boy by Starzl in 1963. This attempt was followed by further adult transplantations till the first successful LT was performed in a child in 1967. Since then we have witnessed a tremendous revolution in the complicated process of LT, which in 1983 was confirmed to be a valid procedure in cases of ESLD in a consensus by the National Institutes of Health. Currently, 1-year patient survival rates for good risk elective cases near to 95% have been reported [1].

Increased awareness of this treatment modality in the developing world has resulted in the establishment of successful pediatric LT in India [2,3]. While the All India Institute of Medical Sciences attempted the first adult LT in 1994, the first successful pediatric and adult LT in India were performed at Indraprastha Apollo Hospital in 1998 in New Delhi [4]. In this article we discuss the recent developments of LT and current status in India.

INDICATIONS

Currently worldwide, King's College [5] and Child's criteria are used for listing patients for LT. Two to three pediatric LT per million people are performed in the west and at this rate two to three thousand children would require LT in India every year. Internationally the most common indications are biliary atresia, fulminant hepatic failure, metabolic inborn errors and non-resectable hepatic tumors. Of 1343 hepatological referrals at our center, 142 fulfilled international criteria. The commonest indications were biliary atresia 69%, followed by fulminant hepatic failure (FHF) 16.9%, cryptogenic cirrhosis 8.4%, progressive familial intrahepatic cholestasis 3.5% and others 2.2%.

Contraindications

Contraindications to LT are active, uncontrollable and untreatable sepsis or multi-system diseases, such as mitochondrial cytopathy or irreversible cardiopulmonary disease, extra hepatic malignancy and active HIV infection unresponsive to highly active antiretroviral therapy.

ASSESSMENT AND PREPARATION

Appropriate patient selection, immaculate preparation and proper timing of transplantation are equally important as the surgical procedure itself for the final outcome. The aims of assessment for LT are (*a*) to confirm the diagnosis and severity of disease, (*b*) to define the patient's general medical status and (*c*) to determine eligibility and priority for transplant. The vascular anatomy of the liver is delineated by doppler ultrasonography and in special situations by magnetic resonance or conventional angiography. Assessment of hepatic function, nutritional, cardiac, developmental, psychiatric, and dental status is performed in all children. Immunity to viral pathogens (measles, chicken pox, herpes simplex, CMV and Epstein Barr virus) is documented by examining the sera and any ongoing infection requires treatment.

Pretransplant, adequate time is spent for nutritional augmentation, as 70% of the children presented at our centre for LT were malnourished. Oral intake is often poor and placement of a nasojejunal tube and overnight feeding are frequently required. Vitamin, iron and zinc deficiency is frequently present and is corrected. Rarely, parenteral

nutrition through a peripherally inserted central catheter is provided. Hepatic complications like ascites, fluid retention and bleeding varices are managed and children with hepatic encephalopathy are treated with low protein diet, bowel wash and at times with molecular adsorbent recycling system (MARS) [6]. Out of 142 children fulfilling the international criteria, 86 were found to be fit for surgery but only 30 families were willing for LT. Among the 56 eligible children that were refused surgery by their families, 40 were girls and 16 were boys. This underlines the bias towards the female child in our social setting, since most families do not want to invest the cost of transplantation on the girl child. Out of the 58 that were unfit, 38 infants with neonatal cholestasis syndrome had severe malnourishment and 22 children also had severe uncontrolled infection. Of the other 20 children with FHF, 10 had multiorgan failure, 9 had sepsis and one had ataxia.

SELECTION OF DONOR

Of the 30 families wiling for LT, 17 families opted for cadaveric transplantation at our center. As cadaveric organs are a scarcity in India, only one could receive the cadaveric donor and the others died while on waiting list. Thus, living related donor transplantation (LRDT) is an attractive option if the ideal donor can be chosen. The usual donor is a parent or a relative of the same blood group with adequate volume of the left lobe of the liver. Our donors are assessed for fitness and receive extensive counseling and an authorization committee approves all living donors. The prevalence of complications for the living donor is relatively low. Out of our 13 patients who decided for the LRDT option, 11 have been transplanted.

SURGICAL PROCEDURES

Due to the shortage of cadaveric donors in India, our center usually performs LRDT. Increased experience and technical improvement has enabled successful LT of children less than 10 kg.

IMMUNOSUPPRESSION

The usual immunosuppressive regimen consists of Calcineurine inhibitors–Cyclosporin (CsA) or Tacrolimus (Tac) and Prednisolone, with or without Azathioprine or Mycophenolate mofetil (MMF). Although CsA and Tac have been successfully used safely and effectively in children, Tac based immunosuppression is preferred because it has been associated with less acute rejection, less estimated corticosteroid-resistant acute rejection rates and fewer cosmetic side effects such as hirsutism. It also is associated with better long-term graft survival. There is no evidence for an increased risk of lymphoproliferative disease in children treated with Tac [7]. Long-term renal dysfunction may be reduced with the use of induction immunosuppressants, such as Daclizumab, a humanized antibody and Basiliximab, a chimeric antibody and with MMF [8] or Sirolimus in maintenance immunosuppression. The current protocol at our center is Tac with Prednisolone.

Complications

Early recognition and correction of post-transplant complication improves graft and patient survival. These include fluid shifts, electrolyte imbalance, renal dysfunction and hypertension. Primary non-function of the graft is relatively rare (2%-5%) and inevitably needs retransplantation. Postoperative bleeding occurs in 5%-10% of patients. Transplant recipients are at an increased risk for vascular thrombosis, frequent evaluation with Doppler ultrasound to evaluate flow is the norm, to detect it early for immediate intervention. Intravenous low molecular weight heparin and oral aspirin is used to prevent thrombosis at our centre.

Biliary leak and stricture are the most common technical complications occurring in 5%-30% of children. The glutamyltransferase test remains the most sensitive indicator of developing bile duct complications. Acute rejection occurs in 40%-70% of children within the first month, and is treated with methylprednisolone. Steroid resistant rejection is treated with antilymphocyte antibodies. Chronic rejection has been a significant cause of graft loss, occurring in up to 10% of children, but the incidence is decreasing. Histological features include loss of bile ducts and graft arteriopathy. Early treatment with Tac and/or Sirolimus may reverse the changes in some children, but most cases progress to retransplantation. At our centre the common complications were rejection (30%), infection (25%), bile leak (14%) and primary graft non-function (4%).

Infections

The majority of children will have at least one episode of infection in the postoperative recovery period. Risk factors include poor graft function, prolonged intensive care unit stay, ventilator dependence, gut perforation, retransplantation, and the use of antilymphocyte antibodies to treat rejection. Bacterial infections are common within the first 2-4 weeks. Herpes viruses are the most common viral pathogens post-transplant, of which CMV dominates and are frequent causes of late infection. *Herpes simplex* and *Varicella zoster* infections occur within one and three months. Posttransplant lymphoproliferative disorder (PTLD) is more common in Epstein-Barr virus (EBV)-negative than EBV-positive recipients. The overall incidence of PTLD after transplantation is 4%-11%. Candida spp. is the most common fungal infection, while *Pneumocystis carinii* is uncommon.

CAUSES OF LATE GRAFT LOSS AND DEATH

The main causes of late deaths reported are recurrent tumor, either hepatoblastoma or hepatocellular carcinoma, or acute hepatic failure [9,10] The most common cause of late graft loss is noncompliance.

RETRANSPLANTATION

Retransplantation is performed in 15% of children, usually for hepatic artery thrombosis or chronic rejection. If performed electively, patient survival is 80% versus 50% when performed as an emergency. Recurrence of the underlying disease has been increasingly recognized as a cause of graft failure. We had one child who required retransplantation due to primary graft non-function and is doing well 2 years post transplant.

Novel therapies

Long-term graft survival rates, the need for maintaining a continual state of immunosuppression, and their side effects has prompted investigators to develop methods to induce tolerance as a means to eliminate the dependency on immunosuppressive agents and improve outcomes [11,12]. Experimental strategies that can be utilized clinically, include mixed allogeneic chimerism, costimulation blockade, and preconditioning with antithymocyte globulin (ATG) [13].

Hepatocyte transplantation is a potentially promising alternative to whole organ liver transplantation, but use in humans is still limited due to the poor availability of cryopreserved cells, weak initial cell engraftment, and lack of clinically safe procedures that can ensure a growth advantage for the transplanted cells. Recently, successful transplantation of fetal liver slices has been reported in the rat model which could serve as a model for genetic metabolic liver diseases [14]. The major obstruction to xenotransplantation or crosstransplantation are the potential spread of infection from animal to the human recipient and hyperacute and vascular rejection. In the future genetic engineering of a chimeric transgenic animal may make long-term xenograft function a reality.

Outcome of liver transplantation in children

According to SPLIT (Studies in Pediatric Liver Transplantation) registry data current 4-year patient and graft survival rates are 83% and 74%, respectively [15]. Older age and greater recipient height are associated with better outcomes, while FHF and ABO incompatibility are associated with poorer outcomes. The majority of children resume normal growth within a year after liver transplant, and there appears to be a dramatic increase in general energy and activity. In a review of psychological adjustment and quality of life over a 5-year period, all children achieved normal growth velocity and 80% had normal height and weight measurement [16]. Twelve children received LT at our centre out of which 8 have been successful. Our longest follow up is 7 years and our first successful recipient is leading a normal life and attending regular school.

CONCLUSION

Patients with growth failure secondary to liver disease resume growing and there appears to be a general improvement in lifestyle after LT. If children undergo transplant early, before significant, growth or developmental retardation, normal psychosocial development may be expected. Children who have received hepatic grafts enter puberty normally. Successful pregnancies have been reported with both CsA and Tac immunosuppression.

In India the major obstacles include lack of awareness and acceptance of this modality both amongst physicians and the general public as an option for liver failure, high costs, late referrals, need to import drugs and consumables, bias against the girl child and the absence of a reliable cadaver organ supply. Significant progress has been made in India in the last 7 years and most of the obstacles can be overcome in the coming years.

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