LIVER TRANSPLANT IN PAEDIATRICS

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ABSTRACT

Paediatric liver transplantation is a very interesting and challenging field. In the past 2 decades, it has become widely accepted as an established therapeutic measure for managing children with end stage liver disease.

Liver diseases are responsible for less than 1% of morbidity and mortality in the paediatric age group in the tropics. Before the advent of liver transplantation, management of end-stage liver disease in children was largely supportive and generally unhelpful in the long term. Prognosis was also poor. However paediatric liver transplantation has recorded remarkable success since it began; hence it has progressed from being just experimental to a definitive modality of management for many end stage liver diseases. Notable advancements in the area of paediatric liver transplantation are the introduction of living donor grafts, improved micro-surgical techniques, development of immunosuppressive drugs and a better appreciation of the multidisciplinary approach to managing the medical and social issues associated with it.

Sadly, though a few Nigerian centres have performed renal transplant surgeries, liver transplant still poses tremendous challenges that appear insurmountable presently.

HISTORICAL PERSPECTIVE

The first human liver transplant surgery was done in 1963 by Thomas E. Starzl on a 3 yr old child with biliary atresia. The patient died shortly after the surgery .However, in 1967, Starzl performed the first successful liver transplant on an 18 month old child with malignant liver tumor. She died 14 months post surgery due to technical factors and problems due to immunosuppresion. The advent of immunosuppressive drugs such as cyclosporine [discovered in 1963]) and tacronimus [discovered in 1989] have increased the 1 year survival rates to over 90% and 5 year survival rates to over 80% in many centres.

In 1990, the first successful living donor transplant was performed in Australia by Strong**.** At present, there are over 100 centres in the world where transplant surgery is being done.

WHO NEEDS A LIVER TRANSPLANT?

For a child to need liver transplant, a number of factors have to be considered. Amongst this is the consideration that liver transplant should be the best form of therapy available for the diseased condition. The clinical indication for liver transplant must be unambigous. Laboratory test results and socioeconomic factors will also determine whether a child really needs another liver or not.

INDICATIONS

- end stage liver diseases; Biliary atresia(which makes up 50% of all PLT), neonatal hepatits, autoimmune hepatits
- progressive liver disease :viral hepatitis Band C, toxins, acetaminophen, valproic acid
- Disorders of metabolism without acceptable forms of treatment; Wilson's disease, alpha 1 antitrypsin deficiency, tyrosinemia
- Unresectable hepatoblastomas without extrahepatic disease
- Indicators of hepatic decompensation (End stage disease)

Clinical indices	Laboratory Indices
Encephalopathy	Intractable hypoglycaemia
Rapidly shrinking liver	Elevated alkaline phosphtase and aspartate transaminase from liver function tests
Rapidly enlarging liver	Elevated PT and PTTK
Deepening jaundice	Hyperbilirubinemia

CONTRAINDICATIONS

Liver transplantation is contraindicated in the following conditions; absolute contraindications include presence of acceptable alternative therapy, untreated systemic infection, HIV and untreated malignancies outside the liver. Poor neurological conditions, poor condition of other organs, presence of a disease expected to recur and ethical issues are relative contraindications.

PATIENT SELECTION FOR PAEDIATRIC LIVER TRANSPLANTATION

Several scoring systems have been developed for assessing liver status and determining the urgency and need for liver transplantation [and most try to address the problems faced by liver transplant patients such as matching need with availability]. There is the MELD-model for end stage liver disease system for adults and the PELD-paediatric end stage liver disease.

The **PELD** is based on the risk of patient death within 3 months of not receiving a transplant. Parameters used include the level of patients' albumin, INR, Bilirubin and patients degree of growth failure. The PELD scores range from 6 to 40. When PELD scores tie, the first child on the waiting list is given priority. Patients in the ICU who have a life expectancy of <7 days will be given priority over the "PELD patients" .This new class of patients are classified as status 1.

The transplantation team must also recommend the patient. This team consists of the transplant co- ordinator, a hepatologist, transplant surgeon, a cardiologist, a pulmonologist and the psychiatrist. The social health workers and support groups are also included.

In case of living donor liver transplants; the donor must be willing to part with his liver, he must share blood group with the recipient, he must be willing and able to undergo surgery ,he should be within 18 and 55yrs and will not receive any form of monetary compensation. Non living donors must be declared brain dead except in very rare cases of neurological derangement.

The overall decision depends on the multidisciplinary transplant team and patients' family [they are required to sign an informed consent]. Patients' ability to comply with post paediatric liver transplant medication and instruction is also considered.

THE PROCEDURE; There are two types of liver transplantation; Orthotopic and Heterotopic (auxillary liver transplantation). An orthotopic liver transplant requires 3 stages ; recipient hepatectomy, removal of donor liver and implantation of donor liver at initial site of recipient liver.

ORTHOTOPIC LIVER TRANSPLANTATION

After induction of anaesthesia, a midline incision is made on recipients over the xiphoid process with subcostal extensions bilaterally and the porta hepatis is dissected to ligate the common bile duct and the common hepatic artery. Vascular clamps are placed on the portal vein, Inferior vena cava and Superior vena cava. Veno-venous bypass is made between the Superior vena cava and axillary vein and between the Inferior vena cava and femoral veins and the diseased liver is excised. Removal of donor liver is easier; it is cooled and preserved in ice until it is needed.

Donor liver is implanted by suturing the supra hepatic and infra hepatic vena cava with that of the recipient. Donor porta hepatis is anastomosed with recipient common hepatic artery while bile ducts are anastomosed end to end. The recipient gall bladder is removed. In some cases the bile duct is drained via a T tube and passed to the exterior. In biliary atresia, biliary drainage is achieved via hepatic jejunostomy with a Roux-en Y-limb anastomosis.

HETEROTOPIC LIVER TRANSPLANTATION

In heterotopic liver transplantation, patient's own liver remains within the patient's body while the donor liver is transplanted adjacent to the recipient's. This is indicated more in inborn errors of metabolism such as Criggler Najjer syndrome where liver function is normal except for one genetic defect. The advantage of this is that patient is not dependent on donor liver in cases of rejection.

IMPROVED TRANSPLANTATION TECHNIQUES

Two major problems faced in paediatric liver transplantation are the shortage of donor liver and donor – recipient disparity. Most children that require a new liver are below 2 years of age while most donors are in the school age or are young adults who are victims of accidental death. Methods used to address these include the RSLT (reduced size liver transplant), SLT (split liver transplant) and LDLT (living donor liver transplant).

RSLT; the donor liver is tailored to fit that of the child. Usually segments 2 and 3(left lateral segments) are used for children 8 times smaller than the donor while segments 2, 3 and 4 (left lobe) are used for children 4 times smaller than the donor.

SLT; the adult liver is divided into 2 viable allografts with segment 2 and 3 for children and segments 4 to 8 for adults.

LDLT; the liver is harvested from a living donor usually a family member. Success rate is high (>99%) but questions are raised on the need for LDLT with the risk of donor morbidity and mortality. The first donor died of the procedure. This was first performed by Strong in 1989.

PERI-OPERATIVE CARE IN PAEDIATRIC LIVER TRANSPLANTATION

- PRE- OPERATIVE MANAGEMENT; Adequate preparation is required in the pre-operative phase. The on- going complications of the liver disease should be managed, patient is put on diuretics to manage ascites, α blockers to reduce the blood pressure, lactulose to help clear toxins in a poorly functioning liver. Antibiotics are also given in case of bacterial peritonitis.
- Several tests will be performed to assess patients' condition such as LFT (liver function tests), RFT (Renal function tests), PT, PTTK, FBC, Blood glucose, Urine MCS, Ultrasound scan of the liver , CT scan of the liver. The patient is also screened for HIV and TB.
- POST-OPERATIVE MANAGEMENT: Patient is monitored in the Intensive Care Unit usually for 3-4 days after surgery during which period patient is put on a respirator. Post operative X-rays and PCV are taken. Vital signs are monitored during this period after which patient is taken to the ward.
- IMMUNOSUPPRESSIVE THERAPY. Since graft rejection is a major complication of PLT, the use of immunosuppressive agents is necessary. Sometimes it is commenced before the transplantation. Agents used include Tacronimus, cyclosporine, azathioprine, mycophenolate mofetil, surolimus, Antilymphocyte globulin, Muromonab-CD3, Daclizumab, Basiliximab and steroids. In addition patient should be put on adequate balanced diet.

COMPLICATIONS OF LIVER TRANSPLANTATION

Complications associated with liver transplantation include organ rejection which could be acute or chronic, vascular complications, biliary complications, liver parenchymal complications, localized fluid collection, post-transplantation lymphoproliferative disorders (PTLD), complications due to infection and psychiatric complications.

Organ rejection: 60 to 80% of children will have at least one episode of acute organ rejection. Symptoms and signs include fever, tachypnea, pleural effusion and jaundice. Laboratory tests reveal elevated liver enzymes level and diagnosis is made by graft biopsy and histologic study. Intensified steroid therapy and change in the immunosuppressive agents used may be helpful in the management.

Hyperacute rejection: This occurs within hours of transplantation and inevitably leads to graft death and need for retransplantation. The process is essentially a vasculitis and is caused by antibodies to blood group antigen.

Acute Rejection: The process of cell death takes place from 24hrs to some weeks. Graft destruction is cell mediated. Methyl prednisolone therapy may be helpful

Chronic rejection: In this case, the process of cell death takes months to years. It usually progresses inexorably and the process is poorly understood. A multiplicity of factors is probably involved; immune and non-immune mechanisms, ischaemia, fibrosis and vasculopathy.

Vascular complications: These may manifest with mildly elevated LFT values to fulminant hepatic failure. They are usually due to vessel calibre differences, clamp injury, previous splenectomy , previous porto-systemic shunts and trauma to the intima during surgery . They include hepatic artery stenosis, hepatic artery thrombosis, portal vein stenosis, portal vein thrombosis, IVC stenosis, IVC thrombosis.

Biliary complications: These are the most common complications and include bile leak (usually at the site of the T tube insertion), bile duct stones and mucocoele.

Liver parenchymal complications include liver infarction (due to insufficient vascularization of donor liver post transplantation). Post transplantation lymphoproliferative disease is caused by clonal expansion of B cells that have been stimulated by Epstein-Barr virus following T cell suppression by immunosuppressive therapy. Patients come up with high fever and can develop Non- hodgkins lymphoma. Patients will benefit from chemotherapy or temporary elimination of immunosuppressive therapy.

Infectious complications: are the highest causes of morbidity and mortality post-liver transplantation. They could be bacterial (usually gram positive aerobic bacteria), viral (EBV, CMV, RSV, HSV) or fungal (*cryptococcus, aspergillus*). A number of factors increase the risk of developing infectious complications.

Pre- transplantation factors include underlying bacterial peritonitis, TB, complications due to the liver disease and age. Young children are more susceptible to RSV, CMV, EBV and opportunistic infections as most have not developed immunity.

Intra-operative factors include use of the T tube drainage and contamination of the operative field during surgery.

Post transplantation factors include immunosuppressive therapy and use of in-dwelling catheters. Post-operative prophylactic therapy with gancyclovir and SMZ/TMP (sulphamethoxazole and trimethoprim) has proven helpful.

Psychiatric complications: Evidence suggests that post-liver transplantation patients usually have an exacerbation of pre-existing underlying psychiatric conditions such as emotional and behavioural disturbances due to growth failure, poor school performance and psychosocial issues hence the need for the psychiatrist's support.

CHALLENGES OF PAEDIATRIC LIVER TRANSPLANTATION

The challenges facing paediatric liver transplantation are multifarious and include the limited supply of donor organs in spite of the technical advances to improve organ availability, long term post-operative care, life-long immunosuppressive therapy, late referral, reduced quality of life post-transplantation, socio-economic factors (which make PLT a questionable form of therapy in developing countries where malaria, HIV and infectious diseases are still prevalent).

There is also the question of whether PLT is a justifiable form of therapy considering the huge financial costs involved, especially with respect to developing nations where there are limited infrastructures and logistic difficulties.

SOME ETHICAL ISSUES

- Inavailability of donor grafts for all those who need them.
- Need for lifelong immunosuppression
- With the high incidence of infections and communicable diseases, why carry out the very costly procedure of orthotopic liver transplantation for chronic liver disorders that account for less than 1% of morbidity and mortality now when problems caused by the former issues remain unresolved and health facilities remain poor.
- Psycho-socio-economic issues
- Ethical issues on consent.

CONCLUSION

While advancements in paediatric liver transplantation are on-going, the challenges being faced are still daunting. However paediatric liver transplantation has a future in the tropics. The longest living liver transplant patient has lived over 25 years and liver transplant patients live acceptably normal lives. With improved socio – economic conditions and organized health funding, paediatric liver transplantation has a future in developing nations.

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