



Experience of 100 Living Donor Liver Transplants in Shaikh Zayed Hospital, Lahore, Pakistan

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ABSTRACT

Introduction: Three percent of world's population is suffering from chronic HCV infection and situation in Pakistan is no different. The sequel of chronic HCV infection is end stage liver disease for which liver transplant is the only lifesaving option left for such patients. In Shaikh Zayed Hospital, Lahore we have been doing liver transplant surgery since 2011. The objective of this study was to report the outcome of 100 LDLT from Pakistan's only public sector hospital and to discuss the solutions of potential obstacles which we faced in its development and sustenance. **Subjects and Methods:** We carried out a retrospective study by collecting the files of all the patients who has received liver transplant from August 2011 to May 2016. **Results:** Mean age of the patients was 45.61 ± 9.57 years with a male to female ratio of 4.8:1. Major cause of decompensation was Hepatitis C whereas 10 patients had hepatocellular carcinoma. Thirty (30%) patients had immediate post-operative complications in which the most common complication was wound infection where as 70% patients had uneventful recovery. Donor complication rate was 13%, in which wound infection takes the lead with 6%. Mean cold ischemia time and warm ischemia time were 2.86 ± 0.86 hours and 49.46 ± 5.98 mins respectively. There was no per-operative mortality in any of our recipients and no donor mortality. survival in our recipients was 85% and 15 patients died at 6months follow up. **Conclusion:** Outcomes comparable to international standards were achieved. Studies with longer follow-up are required to demonstrate if comparable long-term outcomes can also be achieved in our population.

Key Words: Living donor liver transplant, End Stage Liver Disease, Chronic HCV Infection, Graft to Weight Ratio, Liver Attenuation Index, Clavien-Dindo Grading System.

INTRODUCTION

Pakistan is a third world country carrying a heavy burden of liver diseases among which hepatitis C takes the lead. With a population of 180 million and a 7% combined burden of hepatitis B and hepatitis C, liver related deaths in Pakistan has reached 2.7% of all deaths¹⁻⁴. For the patients with end stage liver disease liver transplant is the most effective and lifesaving procedure for last 5 decades. Over the years this procedure has evolved due to refinements in surgical techniques, improved post-

operative care, advent of immunosuppressant and new organ preservative fluids¹⁻³

Liver transplant was started in Pakistan in 2011, so Pakistan is in early phase of liver transplant. Reason for not having a Liver transplant program for so long was attributed to cultural and religious beliefs, lack of public awareness, risk of commercialization, nonexistence of financial support system and a small number of centers with facilities for liver surger⁴. LDLT not only require the highest level of technical expertise, but expensive machinery and medicines to achieve the desired results⁵⁻⁸. Liver Transplant in Pakistan is focused primarily in

private sector, as a result a large number of patients with ESLD who cannot afford the high cost of procedure cannot have a liver transplant. This factor has two fold effects on transplantation, one is medical and other is financial.

In such conditions Shaikh Zayed hospital in Lahore Pakistan is one such institute in public sector where we have carried out more than 100 living donor liver transplants and providing the uniform level of primary, secondary and tertiary care.

The objective of this study was to report the outcome of 100 LDLT from Pakistan's only public sector hospital and to discuss the solutions of potential obstacles in its development and sustenance in a developing country so that more transplant centers can open in country and cater the huge burden of ESLD.

METHODOLOGY:

Shaikh Zayed Hospital performed its first transplant on august 13, 2011, till now 107 transplants have been carried out. We retrospectively collected the data of 100 patients who underwent liver transplant in our hospital from 2011 to May 2016, so that a minimum of one year follow up of the patients can be ensured.

This was a retrospective study with no intervention so it was exempted from formal review by ethical committee of hospital and was performed in accordance with declaration of Helsinki.

Donor selection and investigation

All potential donors undergoing liver transplant were in good health and aged between 18 to 50 years, with blood group compatibility, willing to donate and blood relative of the recipient. Evaluation of the donors started with detailed history and examinations and after that Donors underwent a series of investigations before transplant so that the safety of both recipient and donor could be ensured (Table 1). C.T scan along with liver volumetry carried out to delineate the anatomy including the arterial, portal vein and hepatic veins and to identify any variants in anatomy. GRWR calculated and remnant liver

volume also calculated. Liver attenuation index calculated, all patients having LAI more than 15% or less than 5% had liver biopsies. More than 30% remnant liver volume was kept for all donors. MRCP was done to delineate biliary anatomy. After completion of investigations, evaluation by independent physician and informed consent of the donor. Approval sought from ethical committee of hospital and Pakistan Human Organ Transplant Authority.

Recipient investigations and evaluation

After complete history and clinical examination and establishing the indication of liver transplant, recipient undergoes a series of investigations and evaluations which are presented in table 2.

Operative procedure

For surgery donor was shifted first to theater and after performing cholangiogram recipient is shifted to theater and surgery was started.

Donor surgery was aided by central venous line and arterial line for hemodynamic control. A reverse L shaped incision is given, liver was mobilized, cholecystectomy was done and cystic duct used to perform the cholangiogram to delineate the biliary anatomy, porta hepatis dissected out, zone of ischemia identified and liver resection done using CUSA and hanging maneuver, graft of right lobe taken out after transection of right portal vein, right hepatic artery and right hepatic duct and their stumps were closed. Bile leak or biliary stenosis was checked by injecting methylene blue from cystic duct and then performing cholangiogram. Hemostasis was secured and drain placed in right sub phrenic space.

Recipient surgery was aided by cell saver and rapid infuser, and for hemodynamic control peripheral line, central venous line and arterial lines were maintained. A roof top incision or Mercedes Benz incision was given, liver was mobilized, porta hepatis was dissected, and portal structures were identified and divided as high as possible. At times Liver dissection in recipients became very difficult due to huge collaterals around the liver and blood loss in the operative field.

Step 1	Blood test	Grouping, complete blood count, prothrombin time/international normalized ratio, liver function tests, urea, creatinine, electrolytes, urine R/E, HCV antibody, hepatitis B profile (hepatitis B surface antigen), human immunodeficiency virus 1 and 2 screen
	Radiology	Ultrasound abdomen with liver donor protocol, if donor is female than ultrasound abdomen and pelvis, chest x-ray PA view
	Consultation	transplant surgeon
Step 2	Radiology	Triphasic CT scan of liver with volumetry
Step 3	Blood test	Albumin, G6PD deficiency, reticulocyte count, hemoglobin A1c, thyroid function tests, serum ferritin, ceruloplasmin, fasting lipid profile, calcium, phosphate, , hepatitis B core antibody, hepatitis B surface antibody, arterial blood gases
	Immunology	Anti-nuclear antibody, cytomegalovirus IgG, toxoplasma IgG, IgM
	Radiology	MRCP, Doppler ultrasound abdomen, echocardiography, pulmonary function test
	Urine	Complete report, culture and sensitivity
	Consultation	Cardiologist, pulmonologist, dentist, ophthalmologist, Psychiatrist, anesthetist, hepatologist, gynecologist if female, independent assessor

Table 1 Donor Evaluation Investigations

01	Biochemistry	Serum iron, total iron binding capacity, serum uric acid, serum calcium, magnesium, phosphorus, and copper
02	Prognostic index	Calculation of Child and MELD score
03	Imaging	CT chest, liver dynamic and pelvis
04	Cultures	Blood, urine, sputum
05	Vaccinations	Hemophilus influenza, meningococcus, hepatitis B, pneumococcus
06	Tumor markers	Alpha fetoprotein, carcinoembryonic antigen, cancer antigen 125, carbohydrate antigen 19-9, prostate specific antigen, lactate dehydrogenase
07	Immunology	Hepatitis Be antigen and antibody, HBV DNA (quantitative), HCV RNA polymerase chain reaction (qualitative and quantitative), HCV genotype, hepatitis delta antibody
08	Consultations	cardiologist, pulmonologist, dentist, ophthalmologist, Psychiatrist, anesthetist, hepatologist, gynecologist if female, nephrologist, independent assessor

Table 2 Recipient Evaluation Investigations

A temporary porto-caval shunt performed to prevent bowel congestion during the an-hepatic phase. An intraoperative Doppler ultrasound of the liver was performed to confirm the inflow and outflow patency after reperfusion. Saline and methylene blue was injected via the recipient's cystic duct to identify and secure biliary leaks and confirmed by per operative cholangiogram.

Postoperative Management

After the operation both donors and recipients were shifted to the intensive care unit (ICU). Recipients were weaned off ventilation next morning after performing a Doppler's ultrasound to check the patency of liver inflow and outflow. Central venous

pressure was kept between 5 and 10 cm of water. Immunosuppression, primarily in the form of tacrolimus and steroids, was started 24 hours after the surgery, and levels were tested on every second day. A Doppler ultrasound was performed once daily until the third postoperative day. Drains were removed as soon as the output decreased and were not kept for more than 10 days to avoid any infection.

Statistical analysis

Records were reviewed for demographic data, referral and financial sources of patient, etiology of liver failure, graft characteristics, and operative variables were retrospectively noted. History of

smoking and alcohol abuse was noted as well. Information regarding immediate post-operative complications, total stay of the patient in intensive care unit, cold ischemia time and warm ischemia time of the graft and outcome of the surgery was also noted from those files. All grade 3 and above complications on the Clavien-Dindo grading system was included as morbidity⁹. Because of the retrospective nature of the study, it was difficult to ensure inclusion of all grade 1 and 2 complications, and they were not assessed. P value of <0.05 was considered statistically significant. Data was analyzed using SPSS VERSION 16. Frequencies and percentages were calculated for the qualitative/categorical variables like gender, referral, financial source, smoking and alcohol consumption by the patients, arterial and biliary anastomosis, donor and recipient post-operative complications and outcome of liver transplant. Mean value and standard deviation were calculated for all the quantitative variables including age, workup time of patient, duration of surgery, total stay in intensive care unit, cold and warm ischemia time of the graft.

RESULTS

A total of 100 patients had liver transplantation done out of which 83 (83%) were male and 17 (17%) were female. Mean age of the patients was 45.61 ± 9.57 years. 65 patients had decompensated cirrhosis due to chronic HCV infection, 16 patients had decompensated cirrhosis due to chronic HBV infection. One patient had both HBV and HCV infection while 5 patients had both HBV and HDV infection. Ten patients had HCC, one patient had cryptogenic cirrhosis of liver, while 2 patients had Budd Chiari syndrome (table 03). Fifteen patients were smoker (15%) while 85 were non-smoker (85%). Eighty nine percent patients were referred from outdoor patient depart of Shaikh Zayed while 11 were referred from other hospitals of Punjab, KPK and Baluchistan. Eighty three transplants were financed by Government of Punjab whereas 14 were self-financed and 3 were financed by other resources. Only 5 patients had history of alcohol consumption while 93 were non alcoholics. History regarding alcoholism was not available of 2 patients. Mean duration of work up regarding liver

transplantation was 3.23 ± 2.04 weeks. Minimum time taken was one week and maximum was 12 weeks. Estimated GRWR from liver volumetry was 1.2 ± 0.21 (ranging from 0.91 to 2.15). Mean duration of surgery 13.6 ± 2.38 hours. Patients suffered from immediate post-operative complications were 30 while 70 patients had uneventful immediate post-operative period (30% and 70% respectively). Most common complication (10%) was infection which included wound infection, eight patients had respiratory complications, seven patients had liver related complications including bile leakage (3%) and re-exploration due to post-operative bleeding from liver bed, other complications including post-operative myocardial infarction (2%), cerebrovascular accident (1%) and mucor-mycosis (2%) were included in post-operative complications. Mean duration of stay in intensive care unit (ICU) in immediate post-operative period was 8.44 ± 4.49 days. Mean duration for which patient was kept on ventilator support was 20.27 ± 13.3 hours. Mean cold ischemia time and warm ischemia time were 2.86 ± 0.86 hours and 49.46 ± 5.98 minutes respectively. Total surgical duration was 13.6 ± 2.38 hours, minimum duration was 9 hours and maximum was 22 hours. 64% patients had single biliary duct anastomosis, 26% had double duct anastomosis and 10% had ductoplasty and single duct anastomosis, none of the recipients had hepaticojejunostomy. All biliary anastomosis were end to end. In 85 patients right hepatic artery had anastomosis with right hepatic artery of the recipient, 14% had right hepatic artery anastomosis with left hepatic artery of recipient and 1 patient had right hepatic arterial anastomosis with common hepatic artery. None of the patients had hepatic artery thrombosis after surgery. All patients had temporary porto-caval shunt. 87 donors had uneventful recovery in post-operative period whereas 13 had complications including re-exploration (4%) due to bleeding from phrenic vessel (1%), vena caval stitch surface (2%) and cut surface of CBD (1%), 2 patients had bile leakage from cut surface of the liver which was managed conservatively, 6 patients had superficial wound infection and only a single patient had decompensation which was managed with

supportive care and who recovered after prolong ICU stay. There was no per-operative mortality in any of our recipients and no donor mortality, so all the transplants done at our hospitals were successful. One year survival in our recipients was 85% and 15 patients died at 1 year follow up among which 11 patients expired in their post-operative hospital stay due to myocardial infarction(2%), cerebrovascular accident(1%), mucor-mycosis (2%), primary graft failure (1%) and multi organ dysfunction failure (5%) due to pulmonary and renal complications. 4 patients expired after their discharge from the hospital and was attributed to the noncompliance with immunosuppressive medications. 13% patients presented with biliary stricture on their follow-up visits.

Causes of liver disease	No. of cases
HCV	65
HBV	16
HCC	10
HBV + HDV	05
HCV + HBV	01
Budd chiari	02
Cryptogenic liver cirrhosis	01

DISCUSSION

Liver transplantation is the only option left for the patients suffering from end stage liver disease. Transplantation is considered for those patients who are not expected to survive for less than one year with his own liver¹⁰. Majority of the centers across the globe carry out orthotopic liver transplant where liver is harvested from brain dead donor and transplanted to potential candidates on the waiting list. As cadaveric organs are not available in Pakistan due to social and religious believes, here, in our set up, we carry out living donor transplantation in which a healthy, well-motivated family member or close relative donates a part of his or her liver to the candidate. In this study we have reported outcome of 100 cases of LDLT performed in Pakistani population in a public sector hospital and also highlighted several important issues in a developing country with various financial and social restrictions. Retrograde data collection with comparatively shorter duration of follow up is the

limitation of our study as some of the information was missing.

A total of 100 patients, age between 23 to 66 years, got liver transplantation done. Major indication for liver transplantation turned out to be end stage liver disease due to chronic hepatitis C infection (60%) followed by HCC (12.7%) thus indicating the huge burden caused by chronic HCV in our population¹¹⁻¹⁵. Only two patients had history of alcohol consumption showing that alcohol liver disease is not a major contributor to end stage liver disease in our country as compared to western world where alcoholic liver disease (ALD) is the second most common cause of chronic liver disease (up to 50%)^{14,16,17}.

Mean duration of work up was approximately 4 weeks during which a thorough patient evaluation was carried out. Mean time elapsed between the completed work up and transplantation was 6 weeks which is much earlier as compared to the patients which are put on list for orthotopic liver transplant where organ availability is a rate limiting step and may take around two to three years^{7,18}.

The length of stay in ICU after surgery and need for ventilator support depends upon both pre and post-transplant factors. Preoperative metabolic status of the patient, severity of the disease, number of transfusions during and after the surgery, need of inotropic support, development of renal insufficiency or multiorgan dysfunction all contributes to the prolonged ICU stay. The duration of ICU stay in our L.T recipients ranges from 1 to 20 days with a mean duration of 7.5 days while the mean duration of ventilator support was approximately 20 hours¹⁹.

Complications more than 3 on Clavien Dindo grading system were recorded and frequency of immediate post-operative complications was found to be 30%. Whereas 70% patients had uneventful recovery or had minor complications scoring below 2. Complications like wound infection and respiratory were high but it was inevitable as the patients were compromised and were on immunosuppressive. Our post-operative biliary complication rate (13%) is well acceptable and falls in the range coated by other centers of the world²⁰⁻²⁶. Post-operative myocardial infarction (2%), cerebrovascular accident (1%) and mucor-mycosis

(2%) were included in post-operative complications and the main reason for post-operative mortality in our recipients.

Mean duration of warm ischemia time (WIT) in our patients was 49.46 mins while current data from various studies suggest that warm ischemia time should not exceed 30 mins as it increases the chances of post-transplant biliary complications²⁷. However the mean cold ischemia time (CIT) was 2.86 hours (172mins) which is well under the acceptable limit of 18 hours^{28,29}

All of the transplants were successful since there was no per-operative mortality of any donor or recipient. Out of total 100 patients, 85 patients (85%) had successful liver transplantation which is comparable to one year survival rate of 86% in liver transplant centers of USA³².

The reported frequency of hepatic artery thrombosis (HAT) by other centers is between 2% and 12%^{10,21,22}. None of our patients developed HAT or outflow problems. We believe that sound surgical techniques and the routine use of intraoperative Doppler greatly helped in reducing vascular complications^{17,28,30}

We experienced a lot of difficulties in initiating a transplant program in a government based hospital and later sustaining this program. The reason for discussing the problems is to address them before starting any other transplant program in Pakistan or any other developing country so that better results with smooth sustainability can be achieved. Obstacles faced with their solutions are as follows

1. It is necessary to understand the burden of Hepatitis B and C disease in Pakistan and the need of transplant centers because it cannot be addressed effectively without realizing the gravity of end stage liver disease in our population.

2. It was very difficult to convince a government based hospital in such a program which requires a massive investment, takes time to develop, and there are fears of poor outcomes in the beginning especially when the health funds are very low. It was a brave initiative from the government of Punjab and administration of Shaikh Zayed Hospital to believe in such a program and support us throughout the journey.

3. Most important obstacle was to get a well-trained and well qualified team which include not

only the transplant surgeons but well trained anesthesiologist, radiologists, hepatologists, intensivist and dedicated I.C.U nursing staff. With the passage of time we trained our man power.

4. We also feel that a new transplant program in a developing country should have input from established centers. Our doctors and paramedical staff were sent to Apollo hospital, India, to gain exposure to various aspects of LDLT, and transplants in the early phase were performed with their collaboration.

5. In low- to middle-income countries, financial resources are limited. A majority of patients are poor and cannot afford a transplant, which on average would cost them \$45,000. It is important to develop collaboration with various funding agencies and nongovernmental organizations to provide funds for needy patients because it is difficult to cater all patients by government funds.

6. After establishment of transplant center it is imperative to sustain it, for sustainability it is necessary to give proper incentives to the team members at regular intervals so that desired results can be attained. It will not only improve the performance but also the dedication of the team members.

7. Medical and paramedical staff should have opportunities to improve their skills. Visits to other centers, attendance in relevant courses, and presentations at various meetings should be encouraged.

8. In addition, junior doctors should be sufficiently trained to produce future transplant surgeons and fellowships and training programs should be started so that well trained human resource can be produced and new transplants centers started in country.

Developing countries face unique challenges in developing LDLT programs. These can be overcome with careful planning, role identification, and persistence. Studies with longer follow-up are required to demonstrate if comparable long-term outcomes can also be achieved in our population. Given the tremendous burden of ESLD in Pakistan, more centers need to acquire transplantation expertise.

CONCLUSION

Liver transplant is the only treatment option left for end stage liver diseases. Here in Shaikh Zayed Hospital Lahore, majority of the patients had successful live donor liver transplant with good one year survival rate and marks the successful development of LT program in Pakistan. Outcomes comparable to international standards were achieved; still Studies with longer follow-up are required to demonstrate if comparable long-term outcomes can also be achieved in our population. Given the tremendous burden of ESLD in Pakistan, more centers need to acquire transplantation expertise.

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