Ann Natl Acad Med Sci (India), **43(4):** 209-218, 2007

Liver Transplantation : Indian Perspective

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Abstract

India has a large number of patients with end-stage liver disease requiring liver transplantation. Cadaver organ donation has been unable to meet the existing demand and further efforts are required to promote organ donation and ensure optimal utilization. Living donor liver transplantation offers a viable and effective alternative solution to meet the shortage of cadaver organs. Challenges involved in establishing a successful living donor liver transplant programme include acquisition of advanced infrastructure and technical skills, ensuring donor safety and reducing overall costs making it accessible to a larger number of patients. In this article, we present the results of liver transplantation at Sir Ganga Ram Hospital, identify the obstacles faced during the evolution of the programme and outline the strategies adopted in order to overcome those obstacles.

Keywords: liver transplant programme, live donor liver transplantation, Indian perspective.

Introduction

The need for liver transplantation: magnitude of the problem

With a population of over a billion people, India faces an enormous load of liver disease. From the scanty data available, mainly from the WHO, it is estimated that there are over 40 million Hepatitis B virus carriers and 20 million Hepatitis C virus carriers in the country. This translates into a large number of patients with cirrhosis and end-stage liver disease or malignancy. Collected data from

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tertiary hospitals indicate that between 80,000 and 100,000 patients die of liver failure annually in India. Compared to western figures of 12 to 18 liver transplants per million, India has an abysmally low rate of 0.008 liver transplants per million per year.

The need for a live donor transplant programme

Unlike the United States and Europe where bulk of the liver transplants are performed using cadaveric (deceased donor) organs, in India, cadaveric organ donation rate is extremely low. The United Kingdom has about 18 heart-beating deceased donors per million people annually, while Spain has the highest number of organ donors in the world, approximately 30/million. India had 60 deceased donors/year for the entire population from 2002 to 2006, 0.05% of western figures. Of these, only 10-15 livers were used per year.

The Human Organ Transplantation Act has been in existence for over 12 years. Cadaveric organ donation has not increased due to various factors, including lack of awareness regarding brain death and solid organ donation among the general population and physicians, lack of facilities for harvesting, preserving and transporting organs and lack of a national network for listing patients and organ allocation. Though there are various governmental and non-governmental organizations like ORBO, MOHAN, FORTE and HOPE fulfilling some of these roles on a regional basis, there is lack of coordination and cooperation among these agencies. In the First National Consensus Report on Liver Transplantation and Cadaveric Organ Donation, it was suggested that the need of the hour is the creation of an Indian Network for Organ Sharing (INOS) under whose aegis the regional groups should continue to function (1).

While no efforts should be spared to increase cadaveric organ donation and utilization, live donor liver transplant (LDLT) offers a potential hope for survival to the large number of patients with end-stage liver disease (ESLD) awaiting liver transplantation.

Current scenario in India

Recent trends show an increasing number of liver transplants being performed annually. Beginning with one transplant in 1995, approximately 90 transplants were performed in 2006. Over 300 liver transplants have been performed so far in a total of 21 centres, involving 125 deceased donors (DDLT) and 175 live donors. There are 17 centres which have performed less than 10 transplants each, 3 between 10 and 50 transplants, 1 between 50 and 100 transplants and 1 centre over 100 transplants (Sir Ganga Ram Hospital –SGRH) to date.

We present our experience with live donor liver transplantation, highlighting the prerequisites for starting a program,

obstacles faced during the process and techniques adopted to overcome those hurdles.

The SGRH experience

One hundred and four consecutive liver transplants were performed at our institution between January 2002 and November 2006. There were 100 live donor and 4 deceased donor liver transplants. Data are presented as mean and range unless otherwise specified.

Donor results

Demographic data

Of the 100 donors, there were 61 males and 39 females with a mean age of 36.6 years (range 21-57 years). Right lobes were retrieved from 76 donors and left lobes from the remaining 24. Mean graft to recipient weight ratio was 1.1% (0.6%-3.7%). The middle hepatic vein was included with the right lobe graft in 48 of 76 patients.

Mortality and morbidity

There was no donor mortality. None of the patients developed liver insufficiency postoperatively. Two patients required reoperation for bleeding and one required CT-guided drainage for an intra-abdominal collection. One patient developed partial portal vein thrombosis and one developed chylous ascites, both of which responded to conservative management. One patient required readmission in the postoperative period for intestinal obstruction, which was managed non-operatively. Mean hospital stay was 8.3 days (6-18).

Operative details

Mean operating time was 7.9 hours (5.3-11). A mean of 0.8 units (0-8) of blood were transfused. Seventy-seven donors did not require any transfusion.

Follow-up

At a mean of 19.1 months (0.2-55), all are doing well with normal liver function tests. Depending on their vocation, they have returned to normal activity between 4-7 weeks.

Recipient results

Demographics

Of 100 LDLT's, 90 were adult recipients and 10 were children. There were 71 males and 29 females. Mean age was 39.2 years (1-70).

Indications and aetiology

Nine patients underwent emergency LDLT and the remaining 91 were performed electively. Of the 90 patients with chronic liver disease (CLD), fifteen were Child's Class B (12 patients with HCC) and 75 were Childs C. The commonest etiology of end-stage liver disease requiring liver transplant was Hepatitis C virus (27), followed closely by cryptogenic cirrhosis (20) and hepatocellular carcinoma (19). Eleven patients had Hepatitis B virus, 9 had acute liver failure, 7 each had ethanol-induced and cholestatic liver disease, 3 had Wilson's

and one had autoimmune hepatitis. There were no re-transplants.

Patient and graft survival

Overall patient and graft survival was 86% (88/104) while the survival for LDLT alone was 87% (87/100). There was an improvement in survival with increasing experience. Survival was 78% in the first 50 transplants while it increased to 96% in the next 50 transplants.

Operative details

Seventy-six right lobes and 24 left lobes were transplanted. All 10 pediatric and 14 adult patients received left lobes. Mean operating time was 11.3 hours (5.8-25). A mean of 1650 ml (0-9450) of blood was transfused per patient.

Postoperative course

A triple immunosuppression protocol using steroids, tacrolimus and mycophenolate mofetil was used. Regimen was modified according to renal function and blood cell counts. Patients were extubated at a mean of 10 hours. Mean hospital stay was 17.8 days (11-78).

Discussion

A successful liver transplant programme is identified by its caseload and patient survival (2). Taking lessons from our experience at SGRH, we would like to address four areas, which are vital in establishing a successful live donor liver transplant programme. These include

- Expertise in surgery, hepatology, anesthesiology, critical care and ancillary services like radiology, pathology and blood banking.
- Cost
- Adequate infrastructure to handle liver transplants like well-equipped operation theaters with laminar flow, dedicated liver transplant ICU and step-down facility.
- Donor safety and adaptations of the surgical procedure to expand the donor pool.

Expertise

The core team consisting of surgeon, hepatologist, anesthetist and intensivist must have formal training in established LDLT centres. For the others, in an existing tertiary setup with well developed multidisciplinary support, short visiting fellowships will suffice. In a new setup, formal training in clinical microbiology, interventional radiology, conventional radiology and nephrology as applicable to liver transplant is essential.

There are 21 existing centres and 11 more coming up in India. The country already has over 40 trained (>1 year fellowship) surgeons and several centres have sent their core teams abroad for training. Upcoming centres can easily adapt a successfully functioning model. Our programme has had clinical observers from

12 centres in India and 4 centres abroad for training.

Cost

In a cost to company analysis of the last 50 cases, it was observed that the basic cost of LDLT in an uncomplicated case (60% of total cases) is Rs. 10,00,000. The cost in the remaining 40% is Rs. 14,00,000. Our cases are mainly self-funded with smaller numbers being financed by government or corporate employers and insurance companies. Strategies to reduce the financial burden on patients include cost-cutting measures and increased funding by other agencies including insurance companies.

Liver transplantation also puts a great deal of stress on hospital administration. This is not only because of the initial investment, but also the high ongoing expenditure. The cost-benefit ratio tends to be adverse for at least three to four years in any programme across the world. There is also a risk involved that should the results not be satisfactory, a reputed hospital can lose image due to adverse media publicity. That being said, a successful programme not only generates increased direct and indirect revenue for the hospital, but also enhances its image as a tertiary care centre.

Infrastructure

The SGRH Liver Transplant Unit consists of specially designed modular twin operation theatres with laminar flow. Cavitron ultrasonic suction and aspiration (CUSA), Argon beam coagulation, bipolar electrocautery with drip and fluoroscopy are routinely used surgical tools. Facilities for advanced invasive and non-invasive monitoring of patients are available within the operating theatre. These include high volume infusion pumps, continuous central venous pressure and cardiac output monitors, arterial blood gas analysis and thromboelastogram. Continuous renal replacement therapy is also available on demand. There is a dedicated liver ICU with 4 separate patient cubicles each equipped with positive pressure airflow, ventilators and multi-channel invasive and non-invasive monitors. The ICU has a nurse to patient ratio 1.5:1 which is recommended to deliver the high level of intensive care these patients need especially in the first 48 hours after transplant. This also minimizes the chances of cross infection.

Donor safety and strategies for expanding the donor pool

Morbidity and mortality related to donor hepatectomy has remained one of the most contentious issues in LDLT, as it violates one of the fundamental tenets of medicine '*primum non-nocere*'. There are now 14 reported donor deaths worldwide with donor mortality rates ranging from 0.2% - 0.5% for left lobes and right lobes respectively. Many programmes are

reluctant to adopt LDLT due to this reason. However, in the absence of sufficient cadaveric donors to meet the present demand, LDLT has become a necessity rather than a question of choice. Extrapolating from the experience of centres routinely performing LDLT, a morbidity of 20% and mortality rate of 0.5% may be expected from donor right hepatectomy (3). It is unlikely that this figure will decrease significantly considering the magnitude of the procedure. It has been suggested that it takes approximately 50 cases for the learning curve to plateau (4). Our results compare favorably with those from established centres performing LDLT (Table 1) (5).

Table 1 : Comparison of results of the first 100 LDLT's at SGRH with Queen Mary Hospital, Hong Kong (5)

Parameter	Queen Mary Hospital	Sir Ganga Ram Hospital
Mortality	0	0
Blood loss (ml)	608	616
Operating time (hour)	8.9	7.9
Reoperation (%)	3	1
Complications (major %)	11	14
Complications (minor %)	22	20

The available live donor pool can be increased by rejecting fewer donors without compromising on donor or recipient safety.

In our experience, the main reasons for rejection of blood group compatible donors are:

- Unfavourable donor anatomy
- Small donors with small sized livers
- Fatty livers

Strategies we have adopted to circumvent these problems include:

- Innovative reconstruction by using fresh or cryopreserved portal and hepatic veins retrieved from explants as venous extension grafts
- Use of microvascular surgery to anastomose small arteries and ducts
- Improving venous outflow using middle hepatic vein in small sized grafts to avoid graft congestion
- Use of smaller graft to recipient weight ratio grafts in well preserved recipients

- Utilization of livers with macrovescicular steatosis upto 20%, factoring fat content in calculation of graft and remnant volumes

Our experience with the use of some the above strategies are discussed below.

Impact of Middle Hepatic Vein (MHV) inclusion in right lobe LDLT

The issue of whether the middle hepatic vein (MHV) should be included in the right lobe graft is a debatable one. A selective approach based on donor-recipient body weight ratio, right lobe-to-recipient standard liver volume estimate and hepatic venous anatomy has been advocated, demonstrating equally successful outcomes with or without the MHV (6).

We studied the impact of MHV inclusion in right lobe grafts in LDLT performed at SGRH. Between January 2002 and September 2006, 84 LDLT's were performed utilizing 67 right and 17 left lobe grafts. Patients were divided into 2 groups. Group A included 40 patients (61%) with 34 full and 6 partial MHV. Group B consisted of 27 patients in whom the MHV was not included. In these patients, venous drainage of segment 5, 8 or both was reconstructed. Donor outcomes studied included graft weight, operative time, intraoperative blood loss, postoperative serum bilirubin and aspartate transaminase levels on day 3 and 7, INR and hospital stay. Recipient outcome measures included operative mortality, hospital stay, presence of clinical sepsis, operative time and warm ischemia time. The results are summarized in Tables 2 and 3.

Table 2 : Impact of MHV inclusion in right lobe LDLT -Donor results

Parameters	Group A (N=40)	Group B (N=27)	p-value
Mean graft weight (gm)	802.9	747	NS
Mean operating time (min)	8.73	8.46	NS
Mean blood loss (ml)	653	607	NS
Mean ICU stay (days)	4.1	3.5	NS
Mean hospital stay (days)	7.9	7.6	NS
INR at discharge	1.02	1.00	NS
Bilirubin at discharge (mg/dl)	3.01	1.9	NS
AST at discharge (IU/dl)	62.78	62.04	NS

Table 3 : Impact of MHV inclusion in right lobe LDLT - Recipient results

Parameters	Group A (n=40)	Group B (n=27)	p-value
Operative mortality (n)	6	6	NS
Mean operating time (min)	634	715	NS
Mean warm ischemia (min)	54	67	**S**
Mean ICU stay (days)	9.8	11.7	NS
Mean hospital stay (days)	24.7	29.8	NS
Clinical sepsis (n)	7	11	S

The conclusions drawn from this study were that in properly selected donors, inclusion of MHV with right lobe liver graft is safe. Recipients with grafts including MHV suffer shorter warm ischemic injury, have lower septic morbidity and have better early graft function.

Impact of graft to recipient weight ratio < 0.8 in LDLT

Adequacy of graft size is a limiting factor in adult-to-adult LDLT. It has been observed that graft function and survival are influenced not only by graft size but also by pre-transplantation disease severity. A graft to recipient weight ratio (GRWR) as low as 0.6% has been demonstrated to be safe in patients without cirrhosis or Child's class A patients (7). We analyzed whether a GRWR of less than 0.8 could be safely used in recipients of adult-to-adult LDLT. Eighty-six consecutive patients undergoing LDLT between July 2004 and November 2006 were included. There were 73 right lobe and 13 left lobe grafts. Donor hepatectomy was performed according to standard techniques and graft weight was measured on the back-table after perfusion with Histidine Tryptophan Ketoglutarate (HTK) solution. Group A consisted of 10 patients with GRWR of <0.8 while Group B consisted of 76 patients with GRWR ≥ 0.8. The reasons for a low GRWR included lack of an alternative donor in 4 patients, inaccurate preoperative CT volumetry in 2 patients, and favorable preoperative status of 4 recipients

(Childs status B). There was no postoperative mortality in Group A. Group B had a mortality of 10% (8/76). This difference was statistically significant (p=0.000, ÷2 test â=0.05). The unexpected better survival of low GRWR patients is likely to be attributable to the small cohort of such patients and their better preoperative status. Table 4 shows the comparative values of mean bilirubin, aspartate transaminase levels and INR on postoperative days 1,3 and 7 between the groups. The conclusions were that in selected recipients, with meticulous surgical technique, ensuring a good venous

outflow and good postoperative care a GRWR <0.8 does not have an adverse impact on early results and operative mortality.

Table 4 : Impact of graft to recipient weight ratio (GRWR) on recipients.

Parameters	Bil Day1	Bil Day3	Bil Day7	AST Day1	AST Day3	AST Day7	INR Day1	INR Day3	INR Day7
Group A (GRWR <0.8), (n=10)	5.5	4.4	5.4	247	129	74	3.1	2.3	1.5
Group B GRWR ≥ 0.8), (n=76)	8	4.8	4.9	263	142	50	2.4	2.3	1.4
p-value	0.342	0.801	0.894	0.855	0.818	0.132	**0.007**	0.866	0.602

Management of donors with fatty liver

Hepatic regeneration has been reported to remain unaffected in grafts with less than 30% macrovescicular steatosis. Steatosis has been seen to disappear immediately on histology in these grafts following transplantation. Major complications were also comparable in patients receiving grafts with and without macrovescicular steatosis (8). Our protocol for assessment of donors with suspected fatty livers involves performing a non-contrast CT scan and calculation of Liver attenuation index (LAI). Donors with LAI more than 5 are accepted for further evaluation. Those with an LAI of between 2 and 5 are accepted provided volumetry demonstrates adequate graft and remnant volume after subtracting 30% from calculated volumes. Donors with LAI of -1, 0 or +1 undergo a percutaneous liver biopsy and are accepted provided there is not more than 20% macrovescicular steatosis. Donors with an LAI of less than -1 are rejected, but in case an appropriate alternative donor is not available, those with an LAI of upto -3 are evaluated with a liver biopsy. Of the 178 donors evaluated for 100 LDLT's performed at our institution 78 were rejected. All the donors fulfilled the basic criteria, which included being related to the recipient, age between 18 and 55 years, body mass index less than 30 and compatible blood groups. Fifty-five donors were rejected for fatty liver (50 on the basis of low LAI, 5 on liver biopsy). Six donors with less than 20% macrovescicular steatosis were accepted. All the six recipients of these grafts are alive with good graft function.

Conclusion

All efforts should be made to promote cadaveric liver transplantation by increasing public awareness about brain

death and organ donation via governmental and non-governmental organizations created for the purpose. The public should also be informed of the excellent results achieved in Liver Transplantation within India to instill confidence among them about the potential of organ donation in saving lives. Meanwhile, it has been possible to establish a viable liver transplant programme based on live donors. Development of further new programmes based on already functioning models is possible. However, live donor liver transplant remains an expensive procedure beyond the reach of the majority. Efforts should be made to increase the affordability of the procedure by reducing costs, engaging insurance companies and development of liver transplant programmes in government institutions.

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