REVIEW ARTICLE

Evolving Trends in Right Lobe Living Donor Liver Transplantation

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Introduction

Liver transplantation is the widely accepted treatment for patients of end stage liver disease. Success of liver transplantation has led to expansion of indications, which has further worsened the shortage of available cadaver donors. There has been very little increase in cadaver livers procured over last few years (1) and this crisis is even worse in countries where there are very few cadaver organs available because of cultural, social and religious constrains. This shortage of organs has given rise to innovative strategies to expand the donor pool.

The development of innovative procedures like reduced-size liver transplantation, split liver transplantation, and segmental liver transplantation are based on thorough knowledge of functional anatomy of liver and its regenerating potential. Living donor liver transplantation (LDLT) was first introduced in 1988 to reduce the pediatric waiting list mortality (2) and the first large successful series of LDLT, in infants using lateral segment, was reported by Broelsch *et al* (3) in 1991. Excellent results in pediatric patients provided inspiration for expansion of this procedure to larger children and adults, especially in countries where availability of cadaveric donors is severely restricted. Extension of LDLT to adults by using left lobe graft (4) which can be safely used in older children or small adults, however it does not provide sufficient mass for most of the adult recipients. Yamoaka *et al* (5) and Lo *et a*l (6) reported the first successful use of right lobe and extended right lobe respectively from living related donor. Marcos (7) published the first series of 25 patients using right lobe liver grafts in 1999. Now adult-to-adult LDLT is the most rapidly growing procedure with results equivalent to cadaver whole liver transplantation. Right lobe liver graft provides sufficient hepatocyte mass to adult recipient, bypasses the severe shortage of cadaver livers, and provides hope to patients who will benefit from an early transplantation especially patients with small hepatocellular carcinoma (HCC) or metastatic slow growing tumors for whom chances of getting a cadaver liver in time are very less. Other advantages of LDLT over cadaver liver transplantation are (i) transplantation can be performed electively, (ii) donors are healthy, hemodynamically stable with normal liver function and (iii) short cold ischemia time with good early graft function, (iv) also permits pre-emptive operation before the development of complications of cirrhosis and portal hypertension.

Donor Selection and Donor Safety

Increasing use of right lobe donation, which subjects a healthy individual to major liver resection, has reopened the ethical debate. Donor morbidity in some series is as high as 40-67% (8). Although it is difficult to assess the magnitude of donor risk but most centers quote mortality between 0.1- 1 percent (9). Increasing mortality on liver transplant waiting list and low morbidity (5-15%) and mortality (<5%) after liver resection in non-cirrhotic livers

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was the basis for deeming this procedure ethically feasible. Morbidity after right lobe donation has decreased with increasing experience (19.4%) (10) but it cannot be eliminated. Higher risk involved in right lobectomy prompted professional societies to issue proposals to alert medical community and to make public aware of relevant issues involved in adult LDLT (11). Donors must also accept the risks of surgery and should agree to donation voluntarily.

A potential donor undergoes extensive evaluation, protocol for which varies among different centers. Aim of this evaluation is to minimize complications in donor and to provide good functional graft to recipient. Therefore, for accurate preoperative evaluation of donor's hepatic parenchyma and vasculature, adequate imaging studies are required. As right lobe constitutes more than 60% of liver volume, adult-to-adult LDLT should be performed with the basis that residual liver volume will be sufficient for donor. In non-cirrhotic liver more than 70% of resection can be well tolerated. Fan *et al* (12) recently reported that residual liver volume (RLV) of 27% can support survival in donors with non-steatotic liver, but the general consensus is that the lowest safe RLV is 30%. Therefore, preoperative documentation of liver volume in donor by volumetry is important both for donor and recipient. Computed tomography (CT) volumetry provides an accurate predictive value for weight of graft (11). Several groups use magnetic resonance imaging (MRI) and 3-D CT for pre-operative donor evaluation, which has similar accuracy as CT for volumetric assessment and can also exclude parenchymal disease and vascular and/or biliary anomalies (13-15). Although MR angiography and 3-D CT have results comparable to conventional angiography for main vessels but the imaging of small vessels is still under evolution. Therefore, some centers routinely perform conventional angiography especially to delineate the arterial supply to segment IV which arises from right hepatic artery in 15-30% and it is important to preserve this artery to decrease donor morbidity (7,16).

Variations of biliary anatomy are encountered in about 40% of living donors and there identification is necessary to prevent inadvertent injury or ligation of bile duct during surgery. MR cholangiography is accurate in delineating biliary anatomy upto first order (bifurcation, trifurcation, or posterior segment duct draining into left hepatic duct) in about 89% of donors.

Another issue of debate is role of liver biopsy for preoperative evaluation of donors. It is routinely performed in some centers to estimate degree of steatosis. Most centers do it selectively in donors who have deranged liver function, significant history of alcohol abuse, body mass index of more than 30%, moderate to severe steatosis on imaging studies, or if the donor has positive hepatitis B serology (HBc Ab+, HBs Ab+, HBs Ag-) (8,17). Other potential candidates for liver biopsy are the potential donors of patients with metabolic disease (urea cycle enzyme deficiency). In these donors genetic study should always be done, as it is a familial trait.

Fatty liver can be excluded with help of imaging studies (ultrasonography and CT scan). If the ratio of CT value of liver and spleen (L:S ratio) on plain CT scan is more than 1.2, it implies there is no steatosis. L:S ratios of 1.0-1.2 and less than 1.0 corresponds to mild and moderate to severe steatosis respectively. However, it is important to consider serostatus of donor for hepatitis B and hepatitis C virus. Individual who is positive for hepatitis B surface antigen or hepatitis C virus antibodies should not be accepted as donor not only because of risk of transmission of disease but also because he himself is at risk in future. Donor shortage has led to wider acceptance of grafts from individuals who test positive for hepatitis B core antibody but are surface antigen negative. Recipients of such grafts should be fully informed about the risk of transmission of disease and need of hepatitis B immunoglobulin in post-operative period (18). ABO incompatibility is another contraindication in most of the transplant centers.

Critical Graft Size in Adult LDLT

Major limitation of adult LDLT is optimal graft volume that can be harvested without compromising donor safety. Graft size is expressed as ratio of graft weight to recipient body weight (GRWR) or graft weight as percentage of standard liver volume (SLV). Hepatic grafts less than 1% of GRWR have reduced metabolic and synthetic

capacity reflected by delayed bilirubin clearance and recovery of coagulation profile (19). A linear correlation exists between these two and both are considered as an acceptable means of expressing the estimated graft weight. Although grafts of 0.59% of GRWR (20) have been successfully used in adult recipients, the acceptable safe GRWR is between 0.8-1.0% (40-50% of SLV). These manifestations of inadequate hepatocyte mass have been labeled as small-for-size syndrome (21) which affects both graft function and survival following transplantation. This is because these small grafts sustain a significant degree of injury due to ischaemia, reperfusion, immunological insult and metabolic debt of recipient. All these factors delay regeneration of graft and this early graft dysfunction predisposes patient to sepsis, increased incidence of variceal bleed and intracranial haemorrhage. Outcome of transplantation not only depends on graft size but also on pre-transplant condition of recipient. Ben-Haim *et al* (22) have reported no significant survival difference in Child class A patient who received small or large grafts (83 vs. 88%), but reported significant difference in survival with Child class B or C (33 vs. 74%) following transplantation. They concluded that transplant recipients with Child class B or C required a GRWR of 0.8% to avoid small-for-size syndrome and related complications. However, Kyushu University group (23) suggests that graft with less than 30% of SLV can be used by making portosystemic shunt intraoperatively for portal vein decompression and by providing liver support postoperatively until graft liver regenerates. Portocaval shunt is an important factor for preventing graft injury after reperfusion as hyperdynamic portal blood might damage a relatively small graft.

Use of marginal graft in a sick recipient cannot be justified in LDLT because there should be a reasonable chance of survival of recipient to justify morbidity of healthy donor. To avoid small-for-size syndrome and to provide adequate graft mass to larger recipients, number of strategies have been proposed . Fan *et al* (12) have described use of extended right lobe with excellent results and low donor morbidity. Auxiliary partial orthotopic liver transplantation (APOLT) is another viable option when native liver retains some functional capability to support during early postoperative period (24). Use of dual grafts from two living donors has also been reported (25).

LDLT in Fulminant Hepatic failure and Hepatocellular

Increasing experience and improving results of adult LDLT have encouraged transplant centers to use this procedure for patients with fulminant hepatic failure (FHF) (26-28). Orthotopic liver transplantation is presently considered to be an acceptable life saving treatment for FHF because results of supportive management are not satisfactory (56-80% versus 15-20% survival) (26). To accept a living donor for patient with hepatic encephlopathy, whose post transplant neurological recovery cannot be guaranteed, is still a matter of debate. It is also demanding for the transplant team to compress donor evaluation to an overnight process and to provide adequate sized graft for successful outcome. Some centers recommend APOLT for cases of FHF (24). This provides an opportunity to stop immunosuppression after the recovery of native liver function. However, portal blood may preferentially flow to native liver compromising the graft function. Also APOLT is technically more challenging and neurological sequels are more common after this procedure.

Liver transplantation is also beneficial for patients with small hepatocellular carcinoma or metastasis in liver without extrahepatic diseases (13,29-33). Long waiting time faced by these patients who already have cirrhotic liver decrease the probability of cure. Ideal candidates for transplantation are the ones with tumor less than 5 cm in size, less than three in number and without extrahepatic spread. In these patients five-year survival of 68% has been reported. Survival mainly depends on vascular invasion, which may be difficult to assess preoperatively. Role of transplantation in multi-focal HCC is controversial. Sallizzoni *et al* (33) have reported 5-year survival of 83% for stage I and II and 55% for stage III and IV multifocal HCC.

Immunosuppression

Tacrolimus is the most commonly used primary immunosuppressant in liver transplantation. Two large multicenteric studies conducted in Europe and USA

confirmed superiority of tacrolimus over cylosporin with respect to lower rates of acute rejection, refractory rejection and chronic rejection. Both tacrolimus based dual (with steroids) and triple (with steroids and azathioprine) drug regimens provide effective and safe immunosuppression (34). Tacrolimus has reduced required dosage of corticosteroids and has enabled transplant centers to withdraw steroids successfully in 6 months to 1 year after transplantation. Some centers have successfully withdrawn all immunosuppression in cadaveric orthotopic liver transplanatation and pediatric LDLT secondary to infection, non-compliance, or electively.

Results of Right Lobe LDLT

Japanese survey has reported five- year cumulative graft survival of 82 & 70 percent for paediatric and adult recipients respectively. Primary non-function is uncommon and technical complications are the most common cause of graft loss. With increasing experience and standardization of technique these results should also improve further.

Conclusion

Right lobe LDLT is a new upcoming approach that is gaining popularity worldwide these days. This procedure came into practice not only to overcome the shortage of cadaver organs but also because of inadequacy of graft size by using left lobe in adult recipients. Safety of donor is well established in experienced hands but optimal graft size for an adult recipient is still a matter of debate. Many centers have proposed minimum desired GRWR of 0.8 to 1.0% to overcome this shortage with acceptable results.

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