Initial Experience with Urgent Adult-to-Adult Living Donor Liver Transplantation in Fulminant Hepatic Failure

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Abstract

Background: The prognosis of patients with fulminant hepatic failure without timely liver transplantation is dismal. Given the limited availability of cadaveric organs for urgent transplantation in Israel, adult-to-adult living donor segmental liver transplantation may be the only alternative.

Objectives: To report our initial experience with urgent lifesaving LDLT in this unique scenario.

Methods: Three adult patients with FHF (two of unknown etiology, one with paracetamol intoxication) were transferred from other institutions and admitted to our intensive care unit. Initial treatment and monitoring included intracranial pressure monitoring and hepatic dialysis using the Molecular Adsorbent Recirculating System. Expeditious potential donor selection included medical, psychosocial and surgical evaluation. Liver volume and vascular anatomic compatibility were assessed with computed tomography angiography.

Results: Between July and October 2003 we performed three procedures of urgent adult-to-adult LDLT. The donors (two uncles, one sister) underwent hepatic resection (two right lobes, one left lateral segment) and recovered well. The recipients underwent total hepatectomy with caval preservation, followed by lobar grafting. All recipients recovered and are alive with good liver function and without any neurologic complications.

Conclusions: Urgent adult-to-adult living donor segmental liver transplantation can be performed safely and timely as a lifesaving procedure in the setting of comatose patients with FHF.

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While the survival of patients with fulminant hepatic failure without liver transplantation is still poor at 15–30% [1,2], the prognosis of FHF has improved dramatically since the introduction of liver transplantation [1]. Because of the rapidly progressive nature of FHF, the need for liver transplantation is urgent. The death rate of patients with FHF who are awaiting cadaveric transplantation is high, 40–60% [3], due to the difficulty and delay in obtaining liver grafts before irreversible damage occurs. The mortality is probably higher in countries where the availability of cadaveric donors is limited.

Living donor liver transplantation is now accepted as an effective treatment for patients with end-stage liver disease. Living donors are the main source of organs in emergency settings in countries where the availability of cadaveric donors is restricted. While the utilization of LDLT for pediatric recipients in this setting is well documented, its application in adults is relatively new and less common. We report our experience with urgent adult-to-adult LDLT in the setting of FHF.

Patients and Methods

Patient 1

- *Clinical course:* An 18 year old girl, weight 45 kg, was transferred to our center with FHF secondary to paracetamol intoxication. Symptomatic liver failure developed rapidly with severe coagulopathy (INR 3, factor V 12%, factor VII <5%), jaundice (total bilirubin 5.3 mg/dl) and grade 4 encephalopathy. The patient was admitted to the intensive care unit and close monitoring of her hemodynamics and intracranial pressure was initiated. ICP maximal levels reached 40 mmHg with only partial response to hepatic dialysis with MARS (Molecular Adsorbent Recirculating System). Simultaneously, the patient was listed for cadaveric transplantation and evaluation of potential living donors was initiated. The final decision to perform LDLT was taken by a joint team of the ICU physicians, hepatologists and the Transplantation Unit staff.
- *Donor selection:* Three family members were evaluated as potential donors by thorough history, laboratory and psychosocial data. CT angiography was performed to evaluate liver volume and vascular anatomy. Two candidates were excluded due to small liver volume or dual arterial supply to the right lobe. The third one, who had suitable lobar volumes and vascular anatomy, was chosen to be the donor. A right lobe graft was selected due to a sizeable accessory left hepatic artery, which complicates left lobe utilization. The donor was informed of the potential risks of the procedure and the success rates for the recipient survival, and an informed consent was acquired.
- *Operations:* The donor and recipient operations were synchronized to minimize the cold ischemic time. Intraoperative cholangiography demonstrated two separate bile ducts to the right lobe. Formal right hepatic lobectomy was completed without inflow or outflow occlusion. The obtained graft weight was 956 g, with a single artery, hepatic vein and portal vein, and two bile ducts. The recipient underwent total hepatectomy with caval preservation followed by right lobe grafting to the orifice of

LDLT = living donor liver transplantation
FHF = fulminant hepatic failure
ICP = intracranial pressure
ICU = intensive care unit

the right hepatic vein. Inflow included end-to-end portal and arterial anastomosis and biliary drainage was done with two hepaticojejunostomies to a Roux-en-Y reconstruction.

Patient 2

- *Clinical course:* A 21 year old female, weight 43 kg, was admitted to another hospital with jaundice and developed FHF 4 days later, with bilirubin 28.8 mg/dl, INR 4.3 and high transaminase levels. Evaluation for possible etiologies was non-conclusive. She was transferred to our center. MARS dialysis treatment was initiated when encephalopathy developed followed by hepatic coma. ICP monitoring revealed levels within the 20 mmHg range. The patient was listed for cadaveric transplantation and the evaluation process of potential living donors was initiated. Hepatic coma, moderately elevated ICP and deteriorating synthetic liver functions (factor V levels < 20%), despite maximal supportive treatment, were the indications to proceed with transplantation.
- *Donor selection:* Three potential donors were evaluated in the same manner as for patient 1. One was excluded because of a fatty liver and a second due to heavy smoking and positive hepatitis B serology. The third candidate's CT angiography demonstrated a moderate-sized liver, normal arterial anatomy and venous drainage but a portal vein triforcation (separate right posterior and right anterior branches). In view of this anatomic variation and with the weight prediction of 350 g, we decided to use only the left lateral segment.
- *Operation:* The donor underwent left lateral segmentectomy including the left portal vein (right of the umbilical fissure). The recipient underwent total hepatectomy and left lateral segment transplantation with venous drainage to the common orifice of the left and middle hepatic veins and end-to-end portal anastomosis. Due to the small diameter of the left hepatic artery, microscope-assisted anastomosis was performed with a microsurgical technique. A single Roux-en-Y hepaticojejunostomy was constructed.

Patient 3

- *Clinical course:* A 22 year old male, weight 50 kg, was transferred to our center with FHF of unknown etiology. Anemia and serologic diagnosis of celiac disease raised the suspicion of autoimmune hepatitis. Hepatic necrosis with marked jaundice (total bilirubin 14.4 mg/dl) and coagulopathy (INR 3.9, factor V 20%) were evident, but in the absence of any findings suggestive of encephalopathy, a cadaveric liver offer was abandoned on the second day of hospitalization. Three days later, a rapid neurologic deterioration occurred and the patient was transferred to the ICU. Close monitoring of the patient's hemodynamics and intracranial pressure was initiated and there was no response to hepatic dialysis with MARS.
- *Donor selection:* The only potential donor was the patient's 26 year old sister, who was brought from overseas. She was evaluated in the same manner as previously described, and aside from some concern about her being factor V Leiden heterozygous, she was considered an appropriate donor. Given the pre- and intraoperative volume assessment of her liver, we chose to procure a right lobe graft.
- *Operations:* Right hepatic lobectomy to the extent of the middle hepatic vein was completed without inflow or outflow occlusion. The graft weight was 605 g, with a single artery, hepatic vein, portal vein and bile duct. Right lobe grafting was done in the same fashion as described previously. Biliary drainage was done with a (right hepatic) duct to (common hepatic) duct anastomosis.

Results

Pair 1

- *Postoperative course, recipient:* Complete recovery from coma without any neurologic sequelae was observed on postoperative day 5. Graft function was normal, with a serum bilirubin level of 2.1 mg/dl on discharge (POD 14).
- *Donor:* The postoperative course of the donor was complicated by a minor bile leak, which resolved rapidly after endoscopic retrograde cholangiopancreatography and papillotomy without stenting. The donor returned to his preoperative functional status within 2 months.

Pair 2

- *Postoperative course, recipient:* Complete recovery of neurologic status was observed on postoperative day 4. Bilirubin levels declined slowly, with some deterioration on POD 6. CT angiography demonstrated a patent hepatic artery and portal vein. Liver biopsy showed moderate acute rejection, and a patient therapy with intravenous methyl-prednisolone reversed the process. The patient was discharged on POD 20, with bilirubin level of 2.3. On follow-up, the liver function tests were all normal.
- *Donor:* The postoperative course of the donor was uncomplicated and he was discharged on POD 6 and returned to normal activities within 1 month.

Pair 3

- *Postoperative course, recipient:* Complete recovery of neurologic status was observed on postoperative day 2. Repeated Doppler tests and CT angiography demonstrated a patent hepatic artery and a patent portal vein. The patient was discharged on POD 8 with normal liver function tests and experienced an episode of reversible acute rejection one week later.
- *Donor:* The donor was discharged on POD 10 but was readmitted due to symptomatic right pleural effusion with rapid resolution of fever and pain after drainage.

Discussion

Fulminant hepatic failure is a life-threatening condition with a formidable prognosis. Advances in intensive care and medical management as well as the development of artificial liver support

MARS = Molecular Adsorbent Recirculating System

POD = postoperative day

systems have led to only modest improvement in outcomes [4–6]. Without liver transplantation the prognosis for patients with FHF is still very poor, with survival rates not exceeding 15–30% [1,2]. The most common causes of death are cerebral edema and sepsis [7]. The survival rates have improved dramatically since the introduction of liver transplantation for this condition, with reported 5 year survival rates of 60–80% [8–10]. However, because the need for transplantation is urgent, the death rate among patients awaiting cadaveric donors is high [3]. In Israel, the availability of cadaveric donors is minimal, and the option of transferring patients abroad for transplantation is limited.

LDLT for FHF has been developed as an alternative to cadaveric liver transplantation. The first successful LDLT in an adult patient with FHF was reported in 1994 [11], however it is still considered an uncommon procedure. The application of LDLT in FHF raises several issues: donor candidates may have to be selected without the necessary constraints due to the short time available for decision-making. Graft volume may be insufficient in a partial liver transplantation, and careful recipient selection is required to assure a strict indication for liver transplantation with maximal chances of neurologic recovery. Predicting whether a patient with FHF will require transplantation or will recover with medical management alone is difficult. Many studies have attempted to identify prognostic indicators in patients with FHF that will support this clinical decision [12–14]. As in most transplant centers, we considered acute liver failure that was complicated by hepatic encephalopathy (grade 3 or more) resistant to full medical treatment (including MARS and under ICP monitoring), and with worsening synthetic liver function tests as an indication for urgent liver transplantation.

It is also important to consider the recipient's prognosis especially when living donation is considered and donor morbidity is an issue. Extremely poor prognosis may be considered a contraindication for LDLT. Farmer et al. [15] reported their experience with 206 liver transplantations for FHF, and concluded that serum creatinine, time from onset of jaundice to encephalopathy, and INR predicted patient outcome. However, even the group with the *worse* prognosis had a 40% chance of survival, which is considerably higher than without liver transplantation. Signs of irreversible neurologic damage on CT, ICP monitoring or electroencepahalogram are weighted as contraindications to liver transplantation. Continuous ICP monitoring in the comatose patient is crucial. Although it is involved with an invasive procedure, it can direct hemodynamic and pharmacologic manipulation to optimize the cerebral perfusion pressure and can also assist in the selection of candidates. In patients with prolonged fixed increased ICP the neurologic prognosis is dismal and the justification for transplantation should be carefully considered.

The efficacy and value of MARS dialysis in supporting the patient with a failing liver is controversial. Data from large-scale prospective studies are not yet available. However, accumulated international experience demonstrates safety together with potential significant benefits in the setting of acute liver failure [16]. We apply MARS dialysis to all patients with acute liver failure and deteriorated mental status, parallel to listing and preparation for transplantation.

The work-up of potential "elective" donors is generally carried out over the course of weeks. Evaluation under an emergency situation is challenging and requires cooperation between the different services to complete assessment of multiple potential donors within 24–48 hours. It is always important to remember that donor safety in LDLT is a primary measure of success.

Imaging of the vascular anatomy was performed on all potential donors using CT angiography and specific vascular reconstruction. Formal angiography was performed on the selected donor in case 1, but not in the other two. We believe CT angiography is sufficient in most cases, but angiography should be performed when certain anatomic details are not adequately demonstrated CT also allows assessment of liver volume and quality, thereby excluding cases of small livers or significant steatosis.

Informed consent is an important issue. Patients must be given information regarding potential risks, including mortality, as well as the survival chances of the recipient. The donors must be given the opportunity to exclude themselves, and signs of hesitation must be looked for carefully. Meticulous psychological evaluation of the potential donors must be done to assure full understanding of the information given.

The limit of the graft volume is also an issue in LDLT, although the requirement is smaller in the setting of FHF compared to cirrhotic patients. Miwa et al. [17] claimed that minimal graft volume must exceed 30% of the recipient's calculated standard liver volume. Nishizaki et al. [18] compared the postoperative course of patients undergoing LRLT (left lobe) in FHF with small-sized grafts (graft volume/standard liver volume <30%) and medium-sized grafts. They found no significant differences in postoperative complication rates or survival rates between the two groups. We used grafts larger than 30% of the calculated standard volume in all cases.

Conclusion

For the treatment of FHF, in the reality of the organ scarcity in Israel, LDLT may be the only alternative for urgent lifesaving liver transplantation. With competent personnel and adequate institutional capabilities, this highly complex procedure can be performed safely and timely without compromising the donor's safety and with favorable recipient outcome. The medical, technical and ethical complexity of this unique procedure mandates its judicious application following a thorough exclusion of all other alternatives.

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Capsule

Targeting B cells

Immunotherapies for autoimmune diseases and malignancies that involve B cells have focused largely on the removal or inhibition of the offending cells. This tactic has already been effective in treating non-Hodgkin's lymphoma with Rituximab, a chimeric antibody directed at the B cell surface protein, CD20. Despite some success using this mode of therapy, the mechanisms by which B cells are targeted have not been clearly delineated. To explore pathways in anti-CD20 therapy, Uchida et al. generated a panel of murine B cell-depleting antibodies to CD20. The complement system has been considered a prime mediator in anti-CD20 depletion, and, although all the antibodies could kill cells using complement *in vitro*, B cell depletion still occurred efficiently in complement-deficient mice. On the other hand, in mice lacking the Fc receptor (FcR) common gamma-chain, which is used both in complement and cell-mediated cytotoxicity, depletion was significantly compromised. The mechanism of anti-CD20 treatment implicated by these results was confirmed by showing that B cell depletion failed to take place in mice after macrophages had been removed. Defining the roles of FcR-mediated phagocytosis during B cell depletion by anti-CD20 should help refine immunotherapy of B cell-dependent diseases.

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E. Israeli

Capsule

T cell vaccination in multiple sclerosis

Autoreactive T cells against myelin antigens play a pivotal role in the pathogenesis of multiple sclerosis (MS). Achiron and Mandel recently reviewed the concept of T cell vaccination (TCV) as a new treatment modality in MS. In TCV the patient's own activated autoreactive T cells are used after being stimulated with various myelin antigens and attenuated by irradiation, as vaccination. The vaccine T cells stimulate regulatory networks that induce direct depletion of the host pathogenic T cells by CD8+ cytotoxic cells, and initiate CD4+ anti-inflammatory activity. Immunologic data demonstrated that TCV prevented the development of experimental autoimmune encephalomyelitis – the animal model related to MS – and resulted in depletion of myelin autoreactive T cells. Similarly, several clinical trials confirmed the safety and efficacy of TCV in a small number of immunized MS patients, showing a decrease in the relapse rate and accumulation of neurologic disability, which correlated with stabilization of the brain lesion load in brain MRI examinations. Future double-blind, placebo-controlled trials will shed light on the efficacy of TCV early in the disease process, as well as on the attempt to cure the disease by generating regulatory immune networks.

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