Original Articles

Pediatric living-related liver transplantation in Saudi Arabia

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ABSTRACT

Objective: The purpose of this paper is to report our experience of the first 29 consecutive living-related liver transplants in pediatric recipients and to demonstrate the feasibility of living-related liver transplantation in the Arab World. The first living-related liver transplantation in the Kingdom of Saudi Arabia was performed in November 1998 by Bassas et al following an appropriate period of multi-disciplinary preparation.

Methods: This study was carried out at the Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia, during the period November 1998 through to October 2001. A review of the data of the transplanted children and adult donors was carried out. The data recorded for recipients included age, sex, patient's weight, preoperative diagnosis, intraoperative surgical complications, graft size and weight, medical and surgical postoperative complications, immunosuppression, rejection and overall survival rate. Data recorded for the donors included age, sex and any postoperative complications.

Results: The most frequent indication for living-related liver transplantation in our series was metabolic liver disease. Post-operative complications included biliary leaks in 10% (N=3), vascular occlusion in 13% (N=4), acute cellular rejection in 38% (N=11), positive cytomegalovirus PP65 antigen in 38% (N=11), wound infection in 3.4% (N=one), and systemic infections in 14% (N=4). One urgent retransplantation was necessary due to thrombosis of the hepatic artery. Patient and graft survival rates are 96% and 93%. One patient, treated for acute liver failure, died 2 months post-transplant.

Conclusion: Our experience has shown pediatric living-related liver transplantation to be a success whilst alleviating the need for sending Saudi patients overseas for treatment and providing a solution to organ shortages for pediatric patients. In general, this endeavor has broadened the spectrum of our experience in surgery, anesthetics, intensive care and pediatrics.

Keywords: Liver transplant, living-related, split, reduced size.

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Liver transplantation is currently the only curative treatment for end-stage liver disease. It was first performed in the United States of America and subsequently in Europe.[1] In the Kingdom of Saudi Arabia (KSA), the first liver transplant was performed in 1990.[2] The increasing number of indications for transplantation has led to a severe organ shortage necessitating the innovation of new techniques.[3] Size matching of full organ grafts, which used to be a major obstacle for the pediatric population, was tackled in 1984 by Bismuth et al[4] who introduced the reduced size graft technique, but this merely resulted in a shift of organs from the adult to the pediatric pool. In order to better utilize

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cadaveric livers, in 1988 Pichlmayer in Germany developed the technique of split liver transplantation.[5] The survival rate, initially reported as 25%, increased to 70%-90% with improvements in surgical techniques and the introduction of new immunosuppressive agents such as cyclosporin, tacrolimus, mycophenolate mofetil and monoclonal antibodies.[6] Subsequently pediatric liver transplantation became an established and effective modality of treatment for pediatric patients with progressive liver disease, limited only by the scarcity of cadaveric organs. Therefore, living-related liver transplantation (LRLT) was the obvious optimal solution in the pediatric population.[7]

The first pediatric LRLT was performed by Raia et al[8] in 1988 in Brazil, followed by Strong et al[9] in 1989 in Australia. The first series, under strict ethical control, was performed by Broelsch et al. In the Arab world, our group successfully performed the first pediatric LRLT in 1998.[10] Meticulous team efforts to optimize the hospital infrastructure and human resources, together with a multi-disciplinary team approach and the continuous, thorough assessment of problems as they arise has led to the establishment and evolution of our program in the Riyadh Armed Forces Hospital, KSA. This paper reports our experience of LRLT in 29 pediatric recipients.

Methods. The LRLT program at the Riyadh Armed Forces Hospital, KSA commenced in November 1998. All donors were genetically related to the recipients. Two independent psychological consultations were required to confirm the donors' freedom of choice to donate. Data recorded for recipients included age, sex, patient's weight, preoperative diagnosis, intraoperative surgical complications, graft size, medical and surgical postoperative complications, immunosuppression, rejection and overall survival rate. Data recorded for the donors included age, sex and postoperative complications. The donor evaluation consisted of informed consent, medical history, ABO-typing, laboratory analysis, volumetric computed tomographic volume of the left lateral segment of the liver, hepatic arteriograms as well as medical, dental, social and psychiatric evaluations. The left lateral segments II and III of the donor liver were resected using standardized techniques to preserve normal segmental hepatic blood flow. The grafts were all perfused with kastodiol (HTK) solution. The recipients underwent total hepatectomy with the preservation of the inferior vena cava. The left hepatic vein was first anastomosed to the inferior vena cava using the piggyback technique followed by end-to-end anastomosis of the hepatic artery and the portal vein. Finally, the biliodigestive anastomosis using a Roux-en-Y hepaticojejunostomy for biliary drainage was performed after reperfusion of the graft.

Results. The donors, 18 mothers, 7 fathers, one sister, 2 cousins and one uncle, ranged in age from 21 years to 37 years (mean: 27; standard deviation (SD): 5.1) with a hospital stay ranging from 5 to 7 days. The preoperative hepatic angiograms showed suitable arterial anatomy in all patients. The surgical technique for the donors was similar to that used by the Hamburg team.[11] A transient elevation of liver enzymes and serum bilirubin was observed in all donors shortly after surgery. Postoperative complications included an incisional hernia in one donor and biliary leak in another, both of which were surgically repaired. There was no mortality among the donors during the maximum follow-up time of 38.4 months (mean 12.74; SD: 7.3). All of the donors felt that they had made the right choice and that they had made a smooth physical and psychological recovery. The age of the 8 female and 21 male recipients ranged from 10 months to 11 years (mean 3.5; SD: 2.5). Six were younger than one year. The preoperative diagnosis was progressive familial intrahepatic cholestasis (PFIC) in 10, biliary atresia in 7, Crigler-Najjar (type 1) in 3, familial cirrhosis of unknown origin in 5, glycogen storage disease (type IV and I) in one and 2 recipients and one patient with fulminant hepatic failure. **(Table 1)** None of the patients underwent previous abdominal surgery except for 4 patients post-Kasai procedure. The recipients' weight ranged from 4.8 kg-20 kg (mean 11.7; SD: 3.3). All received an ABO compatible transplant. The weight of the graft ranged from 160 gm-300 gm (mean: 215; SD: 36.3) The graft to recipient weight ratio was 1.1-1.3% (mean: 1.2%). The first recipient received cyclosporin while the 2nd recipient initially received cyclosporin, which was changed to tacrolimus following refractory rejection. Subsequently, all patients received tacrolimus for immunosuppression, the dose of which ranged from 0.15-0.7 mg kg^{-1} twice daily to maintain a therapeutic range of 10-15 ng ml^{-1} in the first 3 months then 6-8 ng ml^{-1} in the following period. Concomitant immunosuppression included prednisolone tapered over 6 months in all and mycophenolate mofetil 600mg $(m^2)^{-1}$ twice daily in 3 patients. Side effects of immunosuppression included systemic arterial hypertension in 4 patients which subsequently settled except for one patient with a single kidney who is still receiving treatment; reversible toxic cardiomyopathy in one patient; and metabolic acidosis in one patient, for which a course of treatment over a few months was given. 38% (N= 11) of all patients showed signs of rejection: 4 experienced one episode and 7 multiple episodes. All rejections were confirmed by liver biopsy and treated with methyl prednisolone.

Hepatic artery thrombosis was seen in 2 patients, one of whom had the artery reanastomosed and another who was retransplanted from a cadaveric

Table 1 - Preoperative diagnoses.

Diagnosis	N (%)
Progressive familial intraoperative cholestasis	10 (35)
Biliary Atresia	7 (24)
Crigler Najjar type 1	3 (10)
Familial cirrhosis of unknown etiology	5 (17)
Glycogen storage disease, type 4	1 (3)
Glycogen storage disease, type 1	2 (7)
Acute hepatic failure	1 (3)
Total	**29 (100)**

N - number

Table 2 - Postoperative complications.

Diagnosis	N of patients*
Biliary complications	3
Vascular complications	4
Acute cellular rejection	11
CMV infection**	11
Wound infection	1
Other infections***	4

N - number, CMV - cytomegalovirus
* Any one patient may have experienced more than one postoperative complication
** Patients were asymptomatic (P65 positive only)
*** Including urinary tract infection and respiratory tract infection

donor. In one patient the portal vein was reanastomosed during the transplant procedure due to thrombosis. In one patient with poor liver function, pleural effusion and significant ascites, the liver was repositioned as it was causing kinking of the hepatic vein leading to the complications observed. In 3 patients (10%) with biliary leak the biliary anastomosis was either revised (2 patients) or, the cut surface of the liver was oversewn (1 patient with leak from an accessory bile duct). One of these 3 patients also developed a biliary stricture, which was stented. One patient who developed a wound infection underwent debridement. In another patient intestinal obstruction secondary to an adhesion band was surgically resolved. Other complications in the early postoperative period included hepatic dysfunction (1 patient) which responded to prostaglandin; pleural effusion (3 patients); and respiratory tract infections (4 patients) **(Table 2)**. One patient who experienced fulminant hepatic failure of unknown etiology for 6 weeks before transplantation developed severe brain edema on the 2nd post-operative day. Three weeks after the transplant the liver disease recurred, resulting in hepatic failure and death 8 weeks post transplant, the parents having refused re-transplantation. Liver biopsies carried out pre-operatively and 3 weeks post-operatively showed severe liver necrosis. The delay in transplanting this patient was secondary to the parents' reluctance to the procedure until their eventual consent.

With the exception of one, all of our children were seropositive for cytomegalovirus (CMV) preoperatively. The seronegative child was given a 2-month course of ganciclovir post operatively due to persistent CMV antigenemia. Our policy is not to treat patients prophylacticly with ganciclovir due to the high seroconversion rate in our young population. Cytomegalovirus PP65 antigen test was positive in the first 3 months postoperatively in 11 patients (38%): once in 8 patients (27%), and more than once in 3 patients (10%), none of whom were symptomatic. Whenever the test was positive, the patient was given a 10-day course of ganciclovir (7 mg kg^{-1} per day) until the CMV PP65 laboratory test became negative. There were no cases of post-transplant lymphoproliferative disorder in our series. Polymerose chain reaction (PCR) for Epstein-Barr (EB) virus sent to an outside laboratory was negative in the 2 cases clinically suspected of having post transplant lymphoproliferative disorder (PTLD). At this stage no routine screening for EB virus antigen is carried out routinely in our program. There were no cases of PTLD in our series. There was one death in our series and the remaining 28 patients are still alive 35 months post transplant. One graft failed immediately after LRLT due to arterial thrombosis, which required cadaveric retransplantation. Patient and graft survival rates at 3 years were 96% and 93%.

Discussion. Liver transplantation has significantly reduced the mortality rate of children with liver disease. However, the shortage of cadaveric organs persists in many societies around the world. Prior to LRLT in KSA, children with end-stage liver disease either died or were sent abroad for transplantation. The wide range of liver transplant procedures available, including whole, reduced size, split cadaveric, and living-related has eased the shortage of cadaveric organs and improved the mortality of affected children. Living-related liver transplantation has the advantage of offering the patient a graft of (usually) better quality through elective surgery.[12] In 1982 the Saudi Arabian Committee of Higher Religious Scholars voted in the majority to approve cadaveric and living-related organ donation.[13] In 1983, the same Committee established the Brain Death Law Act.[14] Despite the available Islamic Jurisprudence our society is still reluctant to accept cadaveric organ donation and the reluctance of some religious scholars has had a negative impact on the willingness of families to

donate. In our pediatric intensive care unit, which is a tertiary referral center in KSA, only 4 families agreed to cadaveric organ donation over the last 16 years compared with 29 living-related donors over the last 35 months. There are no hidden financial motives for our living-related transplantation procedures: motivation is borne purely of strong emotional ties between the donors and the recipients, the reward being the witnessing of a successful procedure and the improved quality of life which the child enjoys. This demonstrates the importance of LRLT in our society. In our series, the potential donors were screened thoroughly and by maximizing the safety of the donor no major complications were observed. The donors were fully informed regarding the surgery, its potential complications and any available alternative treatment. All donors consented spontaneously and voluntarily with a 2nd consent being obtained to ensure an unforced decision.

The indications for LRLT in our series were: progressive familial intrahepatic cholestasis (10 patients); familial cirrhosis of unknown origin (5 patients); Crigler-Najjar disease type 1 (3 patients); glycogen storage disease (3 patients); biliary atresia (7 patients); and fulminant hepatic failure (one patient). The most common indication for transplantation in our series was metabolic liver disease (16 patients-55%), compared with 7 patients (24%) with biliary atresia. This is in contrast to the available literature where biliary atresia as an indication for transplantation constitutes up to 70% of all cases.[15] The main reasons for transplanting those children with progressive familial intrahepatic cholestasis were jaundice, pruritis and cirrhosis on liver biopsy, despite intact synthetic function. The reasons for transplanting the patient with glycogen storage disorder were failure to thrive and poor control despite dietary management for 10 years before transplantation, and recurrent uncontrolled epistaxis which, on one occasion, was life threatening. The high incidence of metabolic liver disease in our society can be explained by the high rate of consanguineous marriages within some tribes.

At the outset, one of our primary concerns was the avoidance of complications which have been encountered by some, since there is, inevitably, a steep learning curve associated with the establishment of such a complex program. For this reason, an approach staged over several years was chosen. The program's leading surgeon received full fellowship training at the University of Hamburg, Germany during which the capacity and capabilities of our hospital were scrutinized and the identified shortcomings rectified to enable the establishment of a liver transplant unit. Great importance was placed on establishing a team work approach between all the departments involved. The first transplant was performed in the passive presence of specialists from the supporting center in the fields of surgery, anesthesia, pediatrics and pediatric radiology.

Advances in liver transplantation surgical techniques, immunosuppressive treatment and improved postoperative management have increased survival rates dramatically and reduced morbidity. LRLT has become a routine surgical procedure with an expected survival rate of >90%.[16] Ten percent of our patients developed biliary leak but with prompt diagnosis and management there was no major impact on graft and patient survival. Biliary complications remain a primary concern in LRLT.[17] Reding et al[18] report biliary complications in 34% of LRLTs compared with 14% of patients who received cadaveric grafts. Early recognition of biliary leak obviously reduces the incidence of septicemia in already immuno-compromised recipients. The complex and variable anatomy of the biliary ducts in segments II and III of the liver influences the outcome of reconstructing the biliary anastomosis. Only one patient developed biliary stricture during the past 3 years. Thirty-eight percent of the patients in our series developed positive tests for CMV PP65 antigen, despite the fact that none of them had clinical evidence of an acute infection. They were all treated with ganciclovir. Our protocol does not include prophylactic ganciclovir postoperatively. Acute hepatocellular rejection, as described by others, was also an issue in our series.[19] However, all our patients improved with a brief tapered course of steroid therapy. Rejection was observed in the first 3 months post transplantation and became less of a problem with time.

In conclusion, KSA has a high prevalence of hereditary metabolic liver disease partly due to the high incidence of consanguineous marriages in this cultural environment.[20,21] Because of the shortage of cadaveric donors the need for a LRLT program is obvious. The success of such a program reduces the need to send Saudi patients overseas and provides proper follow-up for children transplanted abroad. Personal communication with the Pittsburgh group revealed 50% mortality in Saudi transplanted children in their center due to inadequate follow-up treatment. We have shown that it is possible to start, maintain and expand a pediatric LRLT program with adequate resources in a short time. With multi-disciplinary involvement in the early planning of such a complex treatment modality, aided by continuous teaching, support, self-evaluation and a readiness to learn, a steep learning curve can be achieved. During the past 3 years we have transplanted 29 children with 96% survival of recipients, 100% survival of donors and 93% survival of transplanted grafts.

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