One hundred and thirty-seven living donor pediatric liver transplants at Riyadh Military Hospital

Results and outlook for future

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ABSTRACT

الأهداف: مراجعة نتائج 137 عملية زراعة كبد من شخص حي تم إجراؤها بالمستشفى القوات المسلحة بالرياض (RMH).

الطريقة: أجريت التحاليل الاستعادية لحالات المرضى المنومين والخارجين من مستشفى القوات المسلحة بالرياض – المملكة العربية السعودية. تم جمع البيانات وفقاً للعمر، نوع الجنس، التشخيص، نوع العملية الجراحية، المضاعفات، ونجاة الزرعات والمستقبلين.

النتائج: تم إجراء أول 137 عملية زراعة كبد من شخص حي في 113 شهراً. تراوح العمر ما بين 4.5 شهراً إلى 14 عاماً. بلغ عدد الذكور 84 (61%). كان 112 طفل سعودي. تم استعمال القطعة الجانبية اليسرى كطعم مباين (زرعة) في 135 حالة. تلقى طفل واحد كلاً من الفص الأيسر والأيمن بالكامل. أجريت 6 عمليات جزئية كبدية مساعدة. أجري فحص الاضطراب الإستقلابي الكبدي العائلي للمجموعة الكبرى من الأطفال الذين يحتاجون لعملية الزراعة. كانت أكثر المؤشرات شيوعاً ركود الصفراء العائلي داخل الكبد والانسداد الصفراوي (45 حالة لكل نوع). كانت أعداد المضاعفات الرئيسية كالتالي: تجلط في الشريان الكبدي 8 حالات، تجلط في الوريد البابي للكبد 3 حالات، تضيق في الوريد البابي 3 حالات، تضيق الوريد الكبدي 3 حالات وتضيق في القناة الصفراء لدى 4 حالات. توفي 15 مريض. وثلاث زرعات فقدت ولكن بلغ معدل النجاة الكلي للمرضى 89% وبلغ معدل النجاة للزرعات 86.8%.

خاتمة: تعتبر عملية زراعة الكبد من شخص حي خياراً متوفراً للأطفال الذين يعانون من مرض كبدي في مرحلته الأخيرة. يعتبر مرض الكبد الإستقلابي أكثر المؤشرات شيوعاً في المملكة العربية السعودية. كما يعتبر التبرع من شخص متوفى في حالة نقص والتبرع من شخص حي بديل عملي. تعد حدوث المضاعفات ومعدلات النجاة للمستقبلين والزرعات بمستشفى الرياض العسكري مقبولة.

Objectives: To review the results of 137 living donor pediatric liver transplants performed at Riyadh Military Hospital (RMH).

Methods: Retrospective analysis of the in- and out-patient case notes was carried out. Data were collected regarding age, gender, nationality, diagnosis, type of procedure, complications and survival of the grafts and the recipients.

Results: The first 137 living donor pediatric liver transplants were performed in 113 months. The age range was 4.5 months to 14 years. Eighty-four recipients (61%) were male. One hundred and twelve children were Saudi. Left lateral segment was used as allograft in 135 cases. One child each received full left lobe and full right lobe. Six auxiliary partial orthotopic liver transplants were carried out. Familial metabolic liver disorders made the largest group of children needing transplant. The most common indications were progressive familial intrahepatic cholestasis and biliary atresia (45 cases each). The numbers of major complications are: hepatic artery thrombosis (n=8); portal vein thrombosis (n=3); portal vein stenosis (n=3); hepatic vein stenosis (n=3) and biliary strictures (n=4). Fifteen patients died. Three further allografts have been lost. Thus, the overall patient survival rate is 89% and graft survival rate is 86.8%.

Conclusion: Living donor liver transplantation is a viable option for children with end-stage liver disease. Metabolic liver disease is the most common indication in Saudi Arabia. The cadaveric donor supply is in shortage and living donation is a practical alternative. The incidence of complications and recipient and graft survival rates of the program at RMH are acceptable.

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Liver transplantation has been established as therapy of choice for end-stage liver disease.[1] Tremendous advances in the fields of surgical technique, immunology and supportive medical services have made this procedure a routine rather than an experiment. Survival after the procedure is a norm and not an exception. Although human liver transplantation started in children, early results of pediatric liver transplantation were poor with a survival rate of less than 40%.[2] The shortage of size matched organs also hindered the progress of this specialized field. This problem was tackled with modifications in surgical techniques.[3] Three main modifications, the reduced size liver transplantation, split liver transplantation, and living donor liver transplantation, have made liver transplantation a practical option for the children with immediate survival rates of more than 95%.[4] The first adult and pediatric liver transplantation in the Middle East were performed at Riyadh Military Hospital (RMH), Kingdom of Saudi Arabia (KSA) in 1990 and 1998.[5] This unit has been the only major pediatric liver transplant center in the Middle East. As the supply of cadaveric pediatric organs is extremely limited, the option of living donors was logical alternative for the majority of cases. We have reviewed the first 137 cases of pediatric living donor liver transplants carried out at RMH, from 1998 to 2008, to audit our initial experience.

Methods. Prince Sultan Liver Transplant Unit at RMH, is the only specialized pediatric liver transplant referral center in KSA and nearby countries. The first living donor pediatric liver transplant was carried out on 19 November, 1998. The 137th case was carried out on 15th March 2008. During this period only one case was performed using cadaveric whole liver which was excluded from this study. Ethical approval was obtained from research and ethical committee of the Hospital for the study. Data were collected from retrospective review of the medical records. Data included information on age, gender, nationality, diagnosis, type of procedure, type of allograft, complications, and survival of the recipients and the grafts. Surgical procedures included transplantation of left lateral segment, full left lobe and full right lobe hepatic allografts. The grafts were placed orthotopically. The surgical technique is described previously.[5] Auxiliary partial orthotopic liver transplantations were also performed. Postoperatively the patients were monitored in the intensive care units (ICU). Doppler ultrasound of the hepatic vessels was carried out in the operating room after completion of vascular anastomoses and after closure of the abdominal fascia. Thereafter, scan was carried out twice a day for the first 3 days in the ICU. Immunosuppression included intraoperative steroid injection after reperfusion followed by tapering of the steroids with complete withdrawal at 6 months. Steroids were accompanied with cyclosporine in the first case but all subsequent patients were either started on or switched to tacrolimus. Later 4 recipients were changed from tacrolimus to cyclosporin due to side effects of tacrolimus. Mycophenolate mofetil was used selectively. Induction was achieved with basiliximab in cases carried out after May 2001. Acute rejection was treated using pulse steroid therapy. Cytomegalovirus (CMV) pp65 antigen was checked weekly for 3 months post-transplantation. Positive antigenemia was treated with intravenous ganciclovir until the antigenemia became negative. Oral valganciclovir was then administered for one week.

Results. One hundred and thirty-seven cases were performed in 113 months (**Figure 1**). The mean age was 3-year and one-month (age range, 4.5 months to 14 years). Fifty-nine children (43%) were less than one-year of age (**Figure 2**). There were 84 males (61%) and 53 females (39%). There were 112 Saudi children. Other nationalities are shown in **Figure 3**. Familial metabolic and cholestatic diseases constituted the largest group as indication for the transplant (**Figure 4**). Progressive familial intrahepatic cholestasis and biliary atresia were the most common diseases leading to liver transplantation. The living donor allografts consisted of either left lateral segment (135 grafts), full left lobe (one graft) or full right lobe (one graft). These allografts were placed in orthotopic position in 131 recipients after native hepatectomy. Six patients underwent auxiliary partial orthotopic liver transplants. Our follow-up ranges between 2 months and 113 months. Fifteen recipients died (**Table 1**). Three further grafts have been lost. One patient developed immediate post-operative hepatic artery thrombosis and was retransplanted abroad and is doing well. Second graft failed due to chronic rejection resulting from poor patient compliance. Third graft has failed due to portal venous steal phenomenon. Thus, the overall survival rates are 89% and 86.8% for the recipient and the graft respectively (**Figure 5**).

The complications were technical, infective and immunological (**Table 2**). Hepatic artery thrombosis (HAT) developed in 8 patients. One patient was retransplanted (mentioned above). Four patients have died. In other 3 the event happened late and the patients are being managed with long-term antibiotics to prevent biliary sepsis as the graft function is acceptable. Portal vein thrombosed in 3 patients. Out of these 3, 2 were associated with hepatic artery thrombosis and these 2 patients died. One patient with portal vein thrombosis underwent meso-Rex shunt; thus, the graft was salvaged. Cases of portal vein stenosis have been managed by balloon dilatation by interventional radiologist. One

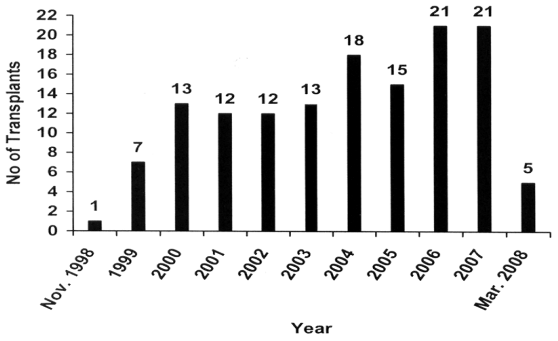

Figure 1 - Number of transplants carried out yearly (graph includes one cadaveric donor case).

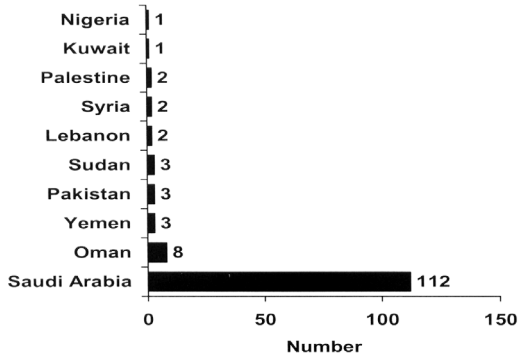

Figure 3 - Transplanted children grouped by nationality.

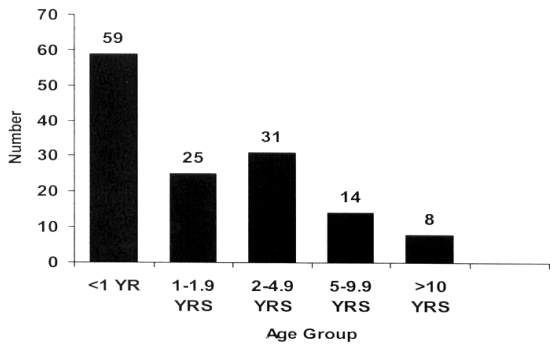

Figure 2 - Transplanted children grouped by age.

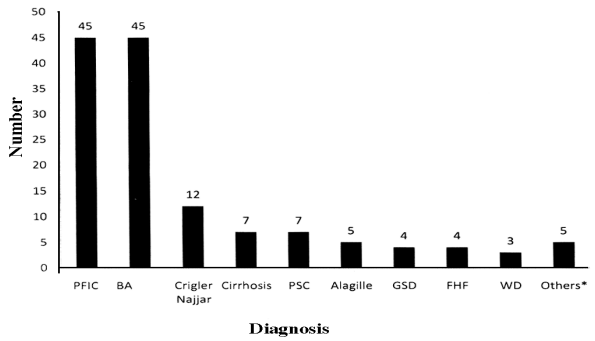

Figure 4 - Preoperative diagnoses. *One case each of cytomegalovirus hepatitis, bile acid synthesis defect, cystic fibrosis, Caroli's disease and factor VII deficiency. PFIC - progressive familial intrahepatic cholestasis; BA – biliary atresia; PSC - primary sclerosing cholangitis; GSD – glycogen storage disease; FHF - fulminant hepatic failure; WD - Wilson's disease.

Table 1 - Death in 15 of 137 patients.

Case number	Age at transplantation	Diagnosis	Cause of death	Time after transplantation
5	3 years	PFIC	Recurrent disease	1 year & 6 months
27	9 months	FHF	Recurrent disease	3.5 months
29	10 months	PFIC	Recurrent disease	11 months
41	11 years	PFIC	HAT, bowel perforation	2 months
42	2 years	Biliary atresia	Pneumonia, viral & fungal infection	4 years
46	2 years	PFIC	Recurrent disease, infection	5 years & 3 months
50	3 years	Biliary atresia, post-Kasai	Generalized oozing	1 day.
71	1 year	PFIC	Fungal infection	8 months
72	7 years	PSC	Massive lower GI bleeding	1 month
95	8 months	Biliary atresia, post-Kasai	HAT, PVT	2 days
106	1.5 years	PFIC	Bronchopneumonia, Gram negative bacterial sepsis	1.5 months
111	2 years	PFIC	HAT	6 months
113	7 months	Biliary atresia, post-Kasai	Generalized oozing, sepsis, MSOF	2 months
118	3 years	Familial liver disease	Adenoviral & fungal infection	4 months
119	5 months	Biliary atresia, post-Kasai	HAT,PVT	4 days

PFIC - progressive familial intrahepatic cholestasis, FHF - fulminant hepatic failure, HAT - hepatic artery thrombosis.
PSC - primary sclerosing cholangitis, GI - gastrointestinal, PVT - portal vein thrombosis, MSOF - multi system organ failure

Table 2 - Post liver transplantation complications.

Complication	Number
Hepatic artery thrombosis	8
Portal vein thrombosis	3
Portal vein stenosis	3
Hepatic vein stenosis	3
Inferior vena cava stenosis with partial thrombosis	1
Bile duct stricture	4
Bile leak	3
Biloma formation	3
Enteric perforation	2
Intestinal obstruction	1
Intra-hepatic arteriovenous fistula	1
Gastric Kaposi's sarcoma	1
Lymphoma	2
De novo hepatitis B	3
Retransplantation	1
Chronic rejection	1
Acute rejection	77

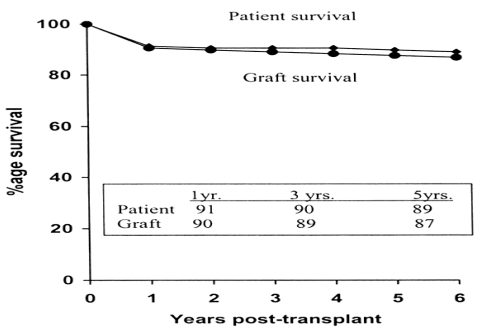

Figure 5 - Overall patient and graft survival.

patient with hepatic venous outflow obstruction required re-operation for re-positioning of the graft as obstruction was positional. Other 2 patients with hepatic venous obstruction were successfully balloon dilated by interventional radiologist. One patient with partial thrombosis secondary to inferior vena cava stenosis was managed successfully by sequential thrombolysis and balloon dilatation. Four patients developed biliary strictures. One patient underwent revision of hepaticojejunostomy. The other 3 were managed by biliary stenting and balloon dilatation with favorable results. Bile leaks were found in 3 patients. Two patients required revision of anastomosis. One patient underwent oversewing of accessory ducts. Postoperative bilomas were noticed in 3 patients and were managed by ultrasound-guided aspiration with or without drainage. Enteric perforation occurred in 2 patients and required re-operation for repair. One patient required laparotomy for intestinal obstruction. One patient developed intrahepatic arteriovenous fistula secondary to core needle biopsy. This resulted in portal hypertension with hemetemesis and splenomegaly. This patient underwent angiographic coiling of the fistula with partial control. Splenectomy has resolved his portal hypertension. Hepatitis B infection has been identified as cause for deranged liver function tests in 3 recipients. The donors have been found to be hepatitis B core antibody positive. These cases were performed during early phase of the program when determination of hepatitis B core antibody status of the donor was not a routine. One patient was diagnosed with gastric Kaposi's sarcoma and responded well to the reduction in immunosuppression. Two patients with post-transplant lymphoproliferative disease are receiving chemotherapy. Acute rejection was diagnosed in 77 children (56.2%) and was treated successfully. No case of CMV disease was identified.

Discussion. Although the first successful human liver transplant was performed in a pediatric patient,[6] the results in this population were initially poor.[2] One major hurdle was shortage of size-matched cadaveric organs. Different technical innovations resulted in the availability of appropriate sized allograft for children. In 1984, Bismuth introduced reduced size liver transplantation (RLT).[7] In RLT, an adult cadaveric organ was tailored to a variety of functional lobes and segments on the back table. However, this technique resulted in a shift of organs from adult to pediatric pool. In 1988, technique of split liver transplant (SLT) was developed.[8] Split liver transplant divided an adult cadaveric organ into 2 functional grafts. The split was carried out either *in-vivo* or *ex-vivo*. Living donor liver transplantation (LDLT) is the logical extension of RLT and SLT. First LDLT was carried out by Raia et al[9] in 1989. The first successful LDLT was reported by Strong et al[10] in 1990. The need for a pediatric liver transplant program becomes obvious by looking at the incidence of liver diseases in children. It is estimated to be approximately one in 2500 live births.[11] Given high growth rate in the KSA, this would translate into a high absolute number of children with liver disease. Before the inception of pediatric liver transplantation program at RMH, these children with end-stage liver disease either died or were sent abroad for liver transplantation. Establishing a liver transplant program is a challenging task.[12] Multi-disciplinary approach is essential for success. A successful program requires trained team, appropriate hospital set-up, supportive administrative back up, and coordination between different services. This challenge was handled in a step-wise fashion. The hospital set-up was scrutinized, prepared, and geared for pediatric liver transplantation while the leading surgeon was trained at the University of Hamburg, Germany. In order to avoid complications faced by a program in the initial phase, some of the cases were performed in the passive presence of staff from University of Hamburg

to extend advice, supervise, and train different medical services involved in the care of these patients.

As mentioned earlier, shortage of appropriate sized allograft for children is an issue. Although the Saudi Committee of Higher Religious Scholars voted in majority to approve the living donation in 1982 and established brain death law in 1983,[5] the society is reluctant to consent for cadaveric organ donation. This is reflected by the fact that in our institution only one patient received a cadaveric organ. In such a situation, LDLT becomes a viable alternative. The living donation has the advantages of better evaluation and preparation of the donor and the recipient, no waiting time for the recipient and procedure in an elective setting. On the other hand, the cadaveric organs expand the donor pool and can be used in emergency situations and whenever there is a need for emergent retransplantation. Metabolic familial liver diseases constitute the most common indication for liver transplant in our program. These include progressive familial intrahepatic cholestasis (PFIC), Crigler-Najjar syndrome, and Wilson's disease. This could be result of referral bias. However, the incidence of metabolic and familial liver diseases might be higher in KSA due to tribal social setup and high rate of consanguineous marriages.[13] Infection was the major or contributory cause of death in our series. This is similar to experience from other centers.[12,14,15] Recurrent disease in allograft after liver transplant in 3 patients for PFIC and in one patient for fulminant hepatic failure led to liver failure and death. Bleeding was a contributory factor in patients who had previously undergone portoenterostomy for biliary atresia. Post-Kasai biliary atresia children may pose challenge to the operating surgeon because of adhesions, underlying liver failure and portal hypertension. It is recommended that patients with biliary atresia should have corrective surgery at appropriate age and in case of failure should be referred for transplantation without any further attempt at revision unless there is clear element of mechanical obstruction.[16,17] The incidences of HAT and other vascular complications are comparable to those reported by other centers.[18,19] Doppler ultrasound is an excellent modality for early detection of vascular complications. Abnormal findings can be confirmed with angiography. Biliary complications are considered Achilles' tendon of liver transplantation. Prompt surgical and radiological interventions are required to prevent infectious catastrophe and ductal problems not amenable to treatment.[20,21] Although it is a retrospective study and is subject to limitations of a retrospective analysis, it shows that pediatric liver transplantation program at RMH started gradually and successfully. In the future, there is a need for research into the etiology of pediatric liver diseases in the KSA. There is also a need for expansion of the program. This should be achieved by expanding the donor pool by educating the society on the cadaveric organ donation. Educating and closely working with primary care physicians and pediatricians to refer the patients at appropriate time would increase the patient load. Multi-disciplinary approach, effective and timely communication, continuous education and training are at the core of a successful program. The need to emphasize on these points by the leadership is required for future progress.

In conclusion, pediatric living donor liver transplant is the treatment of choice for pediatric end-stage liver disease. There is hope of near-normal life after this procedure for the children who suffer from otherwise fatal disease. The procedure is carried out at RMH with acceptable morbidity and mortality. Better results and expansion of the program are anticipated in the future with the strong foundation provided by successful initial experience.

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