ORIGINAL ARTICLE

Early Outcome of Living Donor Liver Transplantation in Children: Analysis of First 17 Cases at Gambat Organ Transplant Program, Pakistan.

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ABSTRACT

Objective: Gambat Living Donor Liver Transplantation (LDLT) Program, Pakistan, started in 2016. Till now,415 LDLT have been performed out of which 17 were Pediatric (18year and less) LDLTs. Except 3 in hospital mortalities, all other children are living comfortable life. The purpose of this study is not only to share our experience of Pediatric LDLT but to analyze our series in order to make future strategies to improve our healthcare provision.

Methods: From March 2019 to September 2020, 17 Pediatric Living donor liver transplants have been performed without any re-transplantation. Early outcome (first six months' post LDLT) of these transplants was observed and analyzed from available data.

Results: In 17 Pediatric LDLTs, three patients died within 30 days post-transplant (82.4 % survival rate). Four patients (23.5 %) re-explored. There was no re-transplantation. In our series, biliary complications rate was 11.8%, hepatic arterial thrombosis rate was 5.88%. In 2 patients, there was more than 1-liter blood loss per operatively, while one patient had significant post-operative blood loss. Intestinal complications 11.8% and T cell mediated rejection was observed in 5.88% which was treated successfully with high dose steroid therapy.

Conclusion: In pediatric LDLT immediate patient survival is very crucial aspect. Good long-term outcome with excellent quality of life is the ultimate goal.

Keywords: Living Donor Liver Transplantation, pediatric population, early outcomes

INTRODUCTION

Liver transplantation (LT) is a lifesaving and milestone development for children with end stage liver disease (ESLD) [1-3].Living donor liver transplantation (LDLT) was originally developed as a solution to organ shortage for pediatric recipients, but it has also been recently extended to adult population as well. Improvement in technical refinement, physiological and logistical innovations in live liver donor surgery that has led to the generalization of the pediatric LDLT with marvelous patient and graft survival outcomes [4]. Due to sociocultural and religious factors, LDLT was originally developed and designed to overcome organ shortage due to decreased access to deceased donor organs [5]. In a country which has world's 2nd highest prevalence of one the most important etiology of liver failure leading to need of transplantation, live donation becomes a vital player and option for centers to meet demands of patients requiring liver transplant [6]. There are certain practical and theoretical benefits of LDLT including early replacement of diseased liver before severe clinical decompensation, source for provision of quality grafts through live liver donor (LLD) evaluations and least likelihood of having grafts preservation induced injury to graft with very short cold and warm ischemia times [7,8]. Also, there are certain immunological benefits due to organs or grafts acquired from close relatives' due maximum chances of having strong leukocyte antigen (LA) match [9]. But there is serious ethical dilemma associated with LDLT due to chances of donor morbidity and mortality which should be less than 0.5%**;** while maximizing recipient health benefits [10].

METHODS AND MATERIALS

Between March 2019 to September 2020, out of 238 living donor's liver transplants (LDLT) at Pir Abdul Qadir Jelani, Institute of medical Sciences, Gambat, Sindh, 17 children (18 years old or below) who underwent LDLT. We collected data about age, gender, blood group and indications for liver transplant. Outcomes of liver transplant were recorded in terms of acute/chronic rejection, surgical complications, blood culture positive sepsis and survival.

The criteria for listing liver transplant in patients with CLD included PELD score >10, age<12 years and model for end stage liver disease (MELD) score > 15 in >12 years as per AASLD guidelines [4]. Those patients who fulfilled King's College criteria and revised Wilson's prognostic

index for Wilson's Disease (WD) were listed for LDLT. However, the trend of INR either outside or within hospital was followed before proceeding for LT.

Vaccination against capsular microorganisms done before transplant. Nutritional assessment was done by measuring weight in kg, height in cm and BMI. Patients of CLD with malnutrition were posted for elective LT for optimization of the nutritional status.

As per Human organ transplant association (HOTA), Pakistan guidelines, all transplants were performed with related donors. Blood group matched liver donors were preferred. In the absence of suitable blood group or volume mismatch in the family members, swap transplantation was done, which means paired donor exchange thus benefitting both patients. We performed one Pediatric Swap LDLT performed in our setup up till now.

Immunosuppression protocol in all patients included induction with 500mg methyl prednisolone during an hepatic phase followed by Methyl prednisolone (day 1) 100 mg,(day 2) 80 mg, (day 3) 60 mg and (day 4) 40 mg followed by oral deltacortil 20mg OD for at least 1 month followed by gradual tapering and decrease of dose over 3 months. Tacrolimus observing renal function tests and urine output unless any toxicity was observed to that drug. Tacrolimus cumulative serum level of 7-10 ng/mL was maintained in the very early initial 1-2 months followed by gradual decrease of the dose over next few months to achieve long term suppression levels of 4-6 ng/mL beyond 1-year post-LT, while keeping renal function test and urine output under close observation.

We used broad spectrum antibiotics for anti-bacterial prophylaxis and fluconazole for anti-fungal prophylaxis. Patients who were CMV PCR positive with titer >2000 treated with Intravenous ganciclovir or oral valganciclovir for three months. CMV PCR (quantitative) advised when we suspected viremia. Ultrasound-Doppler for hepatic vasculature was done daily for first 5 days post-LT.

Donors underwent complete medical and physical evaluation as per standard international living liver donation guidelines [7]. We collected data from donors about age, gender, blood group and relation with recipient. Outcomes were recorded in terms of surgical complications, blood culture positive sepsis and survival.

Statistical Analysis: Data was collected and entered in SPSS version 25 on the basis of age, gender, blood group, indications for liver transplant. Outcomes of liver transplant were recorded in terms of acute/chronic rejection, surgical complications, blood culture positive sepsis, CMV hepatitis, re-exploration, re-transplantation and survival. The data was then analyzed using SPSS version 25. Mean ± standard deviation was calculated for quantitative variables like age, BMI and GRWR. Frequencies were calculated for qualitative variables like gender, type of graft and complications. P-value of ≤0.05 was considered statistically significant.

RESULTS

17 (7.14%) pediatric LDLT out of total 238 LDLT are performed during our study period. We evaluated 20 potential donors for 17 LTs, we rejected 3 donors because of not suitable vascular anatomy. The various characteristics of recipients and donors are given in table 1and 2 respectively. Majority (76.5 %) of patients were males. The mean age and weight of the recipients were (5-18) years and (15-55) kg, respectively. Indications for LDLT in patients in our center are given in table 2, and leading cause for LT was Wilson Disease (WD) 35.3 %,followed by HBV related CLD (23.5%) and PFIC (17.6 %).

76.5%, n=13 donors were having same blood group as recipients, but 23.5% (n=4) had non-identical but compatible blood groups, and none had totally incompatible blood groups. The mean hospital stay of donor was 5days without significant post op complications according to Clavien-indo grading. Pretransplant CMV IgG were positive in 100% of the recipients and donors.

Early Survival rate was 82.4 % in our center. Three patients died during the hospital course (17.6%), 1 child having Primary poor functioning (PPF) graft but died from acute cardiac event on 7th post op day. Second patient have had primary nonfunctioning (PNF) graft and sepsis, died on 8th post op day. Third one developed COVID-19 and died due to respiratory failure on 15th day. There was no re-transplantation performed.

Four patients (23.5 %) re-explored, in one arterial re-anastomosis had done for hepatic artery thrombosis (HAT), in second end ileostomy made for enteric perforation that was closed after 10 months after LDLT, In third one fasciotomy performed for DVT and in 4th patient Re-exploration done for heavy hemorrhagic drain.

Table 1: Characteristics of study population (n=17)

		Frequency	Percent
AGE	5-10 YR	8	47.1
	11-18 YR	9	52.9
Weight	10-30KG	10	58.8
	>30	7	41.2
Gender	MALE	12	70.6
	FEMALE	5	29.4
Blood group	IDENTICAL	13	76.5
	COMPATIBLE	4	23.5
INR	>3	4	23.5
	<3	13	76.5
ECOG	I	14	82.4
	III	3	17.6
CTP	CHILD A	0	0.0
	CHILD B	1	5.9
	CHILD C	16	94.1
MELD Na	LESS THAN 9	9	52.9
	FROM 10 TO 19	2	11.8
	FROM 20 and above	6	34.2

Table 2: Etiology of liver transplantation of study population (n=17)

	Frequency	Percent
HBV/CLD	1	5.9
HBV/HDV/CLD	3	17.6
ALF	1	5.9
WD with ALF	2	11.8
BCS	2	11.8
PFIC	3	17.6
WD without ALF	4	23.5
Cryptogenic (Non-Hepatitis B, Non- HepatitisC)	1	5.9
Total	17	100.0

The biliary complications (post LDLT stricture) rate is 11.8 % (Table 4), arterial thrombosis rate is 5.88 %. In 2 patients more than 1-liter blood lost per operatively, while one patient (5.88 %) re-explored due to significant blood

loss post operatively. Intestinal complications rate is 11.8 % and T cell mediated rejection was seen in 5.88 % which was treated successfully with high dose steroid therapy (injection methyl prednisolone 500mg intravenous for three days).

Table 3: Surgical characteristics and demographics of intervention of study population (n=17)

		Frequency	Percent
Graft Type	Right Graft Without MHV	10	58.8
	RIGHT GRAFT WITHMHV	1	5.9
	LEFT GRAFT	4	23.5
	LEFT LATERALSEGMENT	2	13.3
GRWR	0.8-1.0	1	5.9
	>1.0	16	94.1
Arterial Reconstruction	RHA TO RHA	10	58.8
	RHA TO CHA	1	5.9
	LHA TO CHA	4	23.5
	LHA TO LHA	1	5.9
	LHA TO LGA	1	5.9
Venous Reconstructions	RHV	4	23.5
	RHV, IRHV	3	17.6
	RHV, MHV	1	5.9
	RHV, Seg. V	4	23.5
	LHV, MHV	4	23.5
	LHV	1	5.9
Ductal Anastomosis	SINGLE DUCT	16	94.1
	DOUBLE DUCTS	1	5.9

Table 4: Complications of liver transplantation among study population (n=17)

		Frequency	Percent
Arterial	HAT	1	5.9
	NONE	16	94.1
	NONE	15	88.2
Biliary	BILIARY STRICTURE	2	11.8
	NOT SIGNIFICANT	15	88.2
	MALEENA	1	5.9
Gut	TYPHOID PERFORATION	1	5.9
	UPTO 500 mL	8	47.1
	FROM 500 TO 1000mL	7	41.2
Blood Loss	MORE THAN 1000mL	2	11.8
	NONE	16	94.1
	YES	1	5.9
Acute Rejection	PCR IS NEGATIVE	16	94.1
	PCR is positive, hightitter, kept on treatment	1	5.9
CMV	Culture Positive	3	17.6
	Culture Negative	14	82.3
Sepsis	Not needed	13	76.5
	arterial anastomosis	1	5.9
	Due to bleeding	1	5.9
Re- exploration	Fasciotomy Right leg for DVT	1	5.9
	Laprotomy End Ileostomy	1	5.9
	Not needed	10	58.8
	ERCP /UGE	2	13.3
	ASPIRATION	3	20.0
IR PROCEDURES	ASPIRATION,CHEST INTUBATION	1	5.9
	TRANSPLENIC CANULATION FOR TPA	1	5.9

DISCUSSION

Liver Transplantation (LT) is a lifesaving procedure for children with ESLD. Improvement in technical refinement, physiological and logistical innovations in live liver donor surgery that has led to the generalization of the pediatric LDLT with marvelous patient and graft survival outcomes. In majority of our cases, relationship of donor with recipient was 4 sisters and 4 fathers were the donor. The leading cause for LT at our center were Wilson Disease (40 %) followed by HBV related CLD (26.7 %). However, throughout the world major indication for LDLT in children is BA like data from Southern India by Safwan, et al. [11] reported a primary LT in 43% of their series of 58 with biliary atresia. Delayed referral, worldwide liver transplant outcome data and willingness for liver donation for neonates are major limitations in the management and LDLT for children with Biliary Atresia in Pakistan.

Biliary complications especially bile leak and anastomotic stricture have been a major headache and serious problem for partial liver grafts, in our center post LDLT biliary strictures developed in only two patients (13.3 %) but no biliary leakage and this outcome is comparable to the studies from India, where overall reported incidence is 6-27% after LDLT [12].

In our center, incidence of hepatic artery thrombosis was relatively as low as 5.88%, our one patient developed HAT on 4th POD but salvaged by arterial re-anastomosis but 12-31% occurred in some recent studies [13,14]. Similarly, reported incidence for portal vein thrombosis is 12-44% but we had only 5.88 % incidence only one patient with Budd Chiari Syndrome developed PVT that was managed successfully with trans-splenic catheterization and administration of TPA by interventional radiologist. One patient 5.88 % had Post LDLT enteric perforation.The incidence for CMV infection was 5.88 % in our series as compared to 4-15% of western literature [15]. Blood culture positivity rate and sepsis was 13.3% compared to 20% from data from Chennai, India [16].

Incidence of acute rejection in LDLT reported to be 15-29% [17] while in our acute (T cell mediated) rejection was seen in one patient (5.88 %), which showed good response to high dose steroid therapy. Keeping in view the start of pediatric LDLT, survival rates in our patients is almost similar to well established pediatric transplant centers in the world [18]. Our centers' overall post pediatric LT survival rate is 82.4%.We followed KCH criteria for ALF. Limitations of our study weresmall number of patients, short duration of assessment and also Post-transplant quality of life and nutritional status not addressed in this study.

We conclude that LDLT is the treatment of choice in children with ESLD, inborn errors of metabolism and ALF. Post-liver transplant morbidity and mortality due to vascular, biliary complications and infections have reduced due to technical and medical advances.

Pediatric LDLT immediate patient survival is very crucial aspect. Pre-operative optimization, per operative technical refinements and post-operative management is very challenging and has great impact on ultimate results. In Pediatric liver transplantation good long-term outcome with excellent quality of life is the ultimate goal. Prolonged outcome and evaluation is needed.

CONCLUSION

In pediatric LDLT immediate patient survival is very crucial aspect. Good long-term outcome with excellent quality of

life is the ultimate goal.

Author's contribution: AG and AWD designed the study. SUD collected and arranged data. SHA and HAI compiled data. AS and AH contributed in statistical analysis of data and writing manuscript.

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REFERENCES

1. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2014;59:112–131
2. Tanaka K, Uemoto S, Tokunaga Y. et al. Surgical techniques and innovations in living related liver transplantation. *Ann Surg* 1993; 217: 82– 91.
3. Ng VL, Fecteau A, Shepherd R, et al. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American Multicenter Registry. *Pediatrics*. 2008;122:e1128–e1135
4. Goyet JD, Hausleithner V, Reding R, et al. Impact of innovative techniques on the waiting list and result in pediatric liver transplantation. *Transplantation* 1993; 56: 1130– 1136.
5. Chen CL. Living donor liver transplantation: the Asian experience. *Transplantation*. 2014; 97:53.
6. Levy GA, Selzner N, Grant DR. Fostering liver living donor liver transplantation. *CurrOpin Organ Transplant*. 2016;21:224–230
7. Emre S. Living-donor liver transplantation in children. *Pediatr Transplant*. 2002; 6:43–46.
8. Chan KL, Fan ST, Lo CM, et al. Pediatric liver transplantation in Hong Kong—a domain with scarce deceased donors. *J Pediatr Surg*. 2009;44:2316–2321
9. Liu LU, Bodian CA, Gondolesi GE, et al. Marked differences in acute cellular rejection rates between living-donor and deceased-donor liver transplant recipients. *Transplantation*. 2005; 80:1072–1080.
10. Steel J, ed. *Living Donor Advocacy: An Evolving Role Within Transplantation*. New York, NY: Springer-Verlag; 2014.
11. Safwan M, Ramachandran P, Reddy MS, Shanmugam N, Rela M. Living donor liver transplantation for biliary atresia — an Indian experience. Pediatr Transplant. 2016; 20:1045-50.
12. Wadhawan M, Kumar A, Gupta S, Goyal N, Shandil R, Taneja S, et al. Post-transplant biliary complications: An analysis from a predominantly living donor liver transplant center. J Gastroenterol Hepatol. 2013;28: 1056-60.
13. Miller CM, Gabriel EG, Sander F, Cal M, Luis M, Tomoharu Y, et al. One Hundred nine living donor liver transplants in adults and children: A single-center experience. Ann. Surg. 2001; 234:301-12.
14. Chardot C, Buet C, Serinet MO, Golmard JL, Lachaux A, Roquelaure B, et al. improving outcomes of biliary atresia: French national series 1986-2009. J Hepatol.2013; 58:1209.
15. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol. 2005;56:155-167.
16. Varghese J, Gomathy N, Rajashekhar P, Venugopal K, Olithselvan A, Vivekanandan S, et al. Perioperative bacterial infections in deceased donor and living donor liver transplant recipients. J Clin Exp Hepatol. 2012;2:35-41.
17. Rao S, D'Cruz ALJ, Aggarwal R, Chandrashekar S, Chetan G, Gopalakrishnan G, et al. Pediatric liver transplantation: A report from a pediatric surgical unit. J Indian Assoc Pediatr Surg. 2011;16:2-7.
18. 28.Byun J, Yi NJ, Lee JM, Suh SW, Yoo T, Choi Y, et al.Long term outcomes of pediatric liver transplantation according to age. J Korean Med Sci. 2014;29:320-7