Transplant Int (1992) 5: 205–208

TRANSPLANT
International

Pediatric liver transplantation from neonatal donors

Itsuo Yokoyama, Andreas G. Tzakis, Oscar Imventarza, Satoru Todo, Adrian Casavilla, Antonio Leggio, and Thomas E. Starzl

Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, 3601 Fifth Avenue, Pittsburgh, PA 15213, USA

Received July 10, 1991/Received after revision November 5, 1991/Accepted December 31, 1991

Abstract. Sixteen recipients of neonatal liver grafts were compared with 114 contemporaneous pediatric recipients of grafts from older donors. Graft and patient survival were worse in the neonatal group although the differences were not statistically significant. Patients with neonatal livers who had no technical complications required a longer time postoperatively to correct jaundice and a prolonged prothrombin time. These functional differences were limited to the 1st postoperative month and the end result was the same as with liver transplantation from older donors.

Key words: Liver transplantation, neonatal liver – Neonatal liver, in liver transplantation

The available liver donor pool has been expanded with the use of grafts from older donors [13, 19]. In liver transplantation in infants and small children, the number of candidates far exceeds organ availability, resulting in significant mortality of patients on waiting lists [4, 23]. Possible options include the use of reduced-size or split liver grafts [1, 2, 7, 8, 12] and the use of livers from neonatal donors. Results of our experience with the use of neonatal livers for transplantation in very small pediatric recipients is herein reported. A minimum of 14 months follow-up is provided.

Patients and methods

The charts of all patients who underwent primary liver transplantation at the Children's Hospital of Pittsburgh under cyclosporine-steroid therapy and had liver grafts preserved with University of Wisconsin solution [7] were reviewed. These transplants took place between October 1987, when University of Wisconsin solution became available to us for clinical use, and September 1989, when FK 506 was introduced as the primary immunosuppressive agent [20]. Follow-up is provided to December 31, 1990, and consequently ranged from 14 to 39 months (median 25 months).

One hundred and thirty patients were studied; their primary liver disease is shown in Table 1. The recipient age ranged from 1 to 204 months (mean 51.1 ± 4.9 months) and the male/female ratio was 7/6.

Correspondence to: T. E. Starzl

Two groups were identified depending on the age of the donor: group A were recipients of neonatal (age 28 days or less) donor grafts ($n = 16$) and group B recipients of grafts from older donors ($n = 114$). In case of retransplantation, the age of only the primary donor was considered.

Donor age, body weight, prothrombin time, serum total bilirubin and alanine aminotransferase (ALT) were recorded. These laboratory data were missing for 10 donors in group B.

An accounting of the donors and recipients in group A is given in Table 2. Anoxic injury due to birth asphyxia was the most common cause of donor death (75%). Thirteen donors (81%) were less than 2 weeks old and all weighed less than 5 kg. All but two recipients were less than 1 year old and all weighed less than 10 kg. Biliary atresia was the underlying disease in 11 patients. Nine of them (82%) had had previous failed portoenterostomies.

A summary of the donor and recipient demographic data in group B is shown in Table 3.

The surgical techniques employed for graft recovery and transplantation have been reported previously [14, 16, 18]. Organ preservation period (cold ischemic time) ranged from 6.7 h to 17.9 h (9.4 ± 1.4 h) in group A and from 5.1 h to 29.1 h (8.5 ± 0.5 h) in group B. No statistical differences were noted between the two groups.

Heparin (50 IU/kg subcutaneously twice a day), aspirin (20 mg for body weight < 8 kg, 40 mg for 8–15 kg, or 80 mg for > 15 kg, orally, once a day) and Persantine (dipyridamole, 6.25 mg for body weight < 12 kg or 12.5 mg for ≥ 12 kg, orally, twice a day) were administered, unless bleeding occurred, when the prothrombin time was less than 20 s throughout the hospitalization. All of the patients in group A received parenteral hyperalimentation including vitamin K immediately postoperatively until they tolerated oral feeding well.

Doppler ultrasonography was performed routinely within 24 h postoperatively and was repeated when a complication was suspected. Absence of arterial pulsations on two consecutive ultra-

Table 1. Indications for liver transplantations ($n = 130$)

Diagnosis	No. of patients
Biliary atresia or other type of biliary cirrhosis	85
Cirrhosis secondary to metabolic disorders	15
Chronic hepatitis	13
Postnecrotic cirrhosis	9
Tumors	6
Budd-Chiari syndrome	2
Total	130

Table 2. Donor and recipient patient characteristics in group A (neonatal donors). ICH, Intracerebral hemorrhage; SIDS, sudden infant death syndrome; BA, biliary atresia; ATD, α_1-antitrypsin deficiency; NH, neonatal hepatitis; AS, Alagille's syndrome; PNC, postnecrotic cirrhosis

Donor				Recipient					
Patient no.	Age (days)	Body weight (kg)	Cause of death	Age (months)	Body weight (kg)	Sex	Liver disease	Retrans-plantation	Outcome
1	8	3.7	Anoxia	7	5.6	M	BA	No	Alive
2	20	2.3	Anoxia	6	8.1	M	BA	No	Dead
3	12	3.2	ICH	9	7.3	M	ATD	Yes[b]	Alive
4	28	4.0	Anoxia	5	5.7	M	BA[a]	Yes	Dead
5	8	3.3	SIDS	7	5.9	F	BA[a]	Yes	Dead
6	3	2.7	Anoxia	2	2.7	M	NH	No	Dead
7	2	2.7	Anoxia	13	7.4	F	BA[a]	No	Alive
8	5	2.6	ICH	7	5.5	F	BA[a]	No	Dead
9	3	3.7	ICH	9	5.4	F	BA[a]	Yes	Dead
10	16	3.2	Anoxia	2	5.8	M	Tyrosinemia	No	Alive
11	6	4.5	Anoxia	12	6.3	M	BA[a]	Yes	Alive
12	2	3.2	Anoxia	11	6.3	M	BA[a]	No	Alive
13	6	3.3	Anoxia	19	7.5	M	AS	No	Alive
14	12	3.2	Anoxia	5	3.6	F	PNC	No	Alive
15	3	3.3	Anoxia	5	6.5	F	BA[a]	No	Alive
16	4	3.4	Anoxia	9	6.7	M	BA[a]	No	Alive
Mean	5.6	3.3		8.0	6.0				
SEM	1.8	0.1		1.1	0.3				

[a] Previous portoenterostomy
[b] Received third graft

Table 3. Summary of donor and recipient demographic data in group B (nonneonatal donors)

	Mean ± SEM	
Donor		
Age (years)	4.9 ± 0.4	(32 days to 42 years)
Body weight (kg)	14.0 ± 1.1	(2.7–68.2 kg)
Recipient		
Age (years)	4.8 ± 0.4	(1 month to 17 years)
Body weight (kg)	18.0 ± 0.1	(4.1–84.3 kg)
Sex (male:female)	62:52	

sound examinations established the diagnosis of arterial thrombosis. In some patients, this diagnosis was made by arteriography or during surgical exploration.

Body weight of the patients in group A was recorded preoperatively and followed for the duration of the study. Control values were obtained from the National Center for Health Statistics percentiles [5].

The patients in each group who survived and had a technically uncomplicated postoperative course were identified (group A1 and group B1, respectively). Ten patients in group B1 were excluded due to incompleteness of data. Body weight, prothrombin time, serum total bilirubin and ALT preoperatively and postoperatively at days 1 through 7 and days 14 and 30 were recorded. The prothrombin time values were not in all cases available for postoperative days 14 and 30. In these cases, the mean of the immediately preceding and the following available values were entered.

All data are presented as mean ± the standard error of the mean ($\bar{x}$ + SEM); differences in the mean were tested using Student's t test or χ^2 for comparison procedure. Actuarial survival rates were calculated by the method of Kaplan-Meier. A P value of less than 0.05 was considered to be statistically significant.

Results

Out of all the 130 patients, 35 died (27%), 6 in group A and 29 in group B. The primary causes of death in these 35 patients are shown in Table 4.

Table 4. Postoperative complications and deaths in 130 patients. HATX, hepatic artery thrombosis; PVTX, portal vein thrombosis

Complications	No of patients (deaths)	
	Group A (n = 16)	Group B (n = 114)
Vascular		
HATX[a]	5 (2)	10 (4)
PVTX	1 (1)	2 (0)
Portal vein rupture	0 (0)	1 (1)
Vena caval occlusion	0 (0)	1 (1)
Biliary[a]	0 (0)	11 (0)
Others		
Perioperative death[b]	1 (1)	6 (6)
Graft nonfunction	1 (1)	6 (3)
Bacterial sepsis	0 (0)	5 (5)
Viral infection	1 (1)	4 (4)
Rejection	0 (0)	3 (1)
Malignancy	0 (0)	3 (3)
Pulmonary hypertension	0 (0)	1 (1)
Total	9 (6)	53 (29)

[a] The incidences are significantly different between the two groups ($P < 0.05$)
[b] Complications including intra-operative death or brain death

Actuarial survival rates at 1, 2, and 3 years postoperatively were 68%, 68%, and 51% respectively in group A and 76%, 74% and 74% in group B (Fig. 1, top). Actuarial 1-, 2-, and 3-year graft survival rates were 56%, 56%, and 38% respectively in group A and 70%, 68%, and 67% in group B (Fig. 1, bottom). None of the differences in patient or graft survival achieved statistical significance (P = 0.37 and 0.19, respectively).

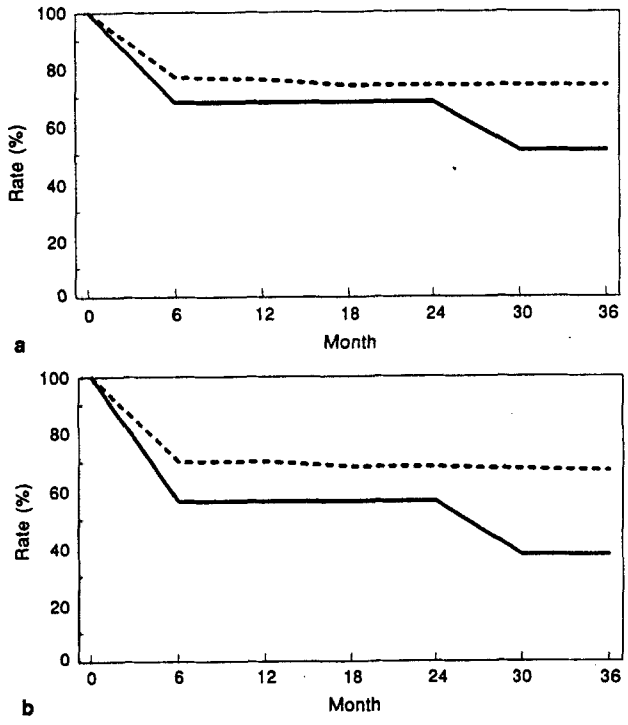

Fig. 1. **a** Cumulative patient survival rates in group A ($n = 16$; donor age ≤ 28 days) and group B ($n = 114$; donor age > 28 days). The difference was not statistically significant ($P = 0.37$). **b** Cumulative graft survival rates in group A and group B. The difference was not statistically significant ($P = 0.19$). — Group A, --- group B

Five patients (31%) in group A underwent retransplantation, due in three patients to hepatic artery thrombosis, in one to primary nonfunction, and in one to hepatitis (Table 2). Two of them were alive at the end of follow-up, including one patient who had a third graft. Nineteen (16%) patients in group B underwent retransplantation, due in ten patients to hepatic artery thrombosis, in six patients to primary nonfunction, and in three patients to rejection. Of them nine were alive at the end of follow-up. Three patients received a third graft; all three died.

Perioperative complications are presented in Table 4. Hepatic artery thrombosis was the most common in group A and its incidence was significantly higher than in group B (31%, $n = 5$ vs 9%, $n = 10$, $P = 0.027$). Of the 15 patients who developed hepatic artery thrombosis nine survived, three in group A, of them one without retransplantation, and six in group B, of them two without retransplantation. Three patients developed portal vein thrombosis: one in group A and two in group B. The patient in group A died as a result of this complication. Both patients in group B were alive, one after successful thrombectomy and one other after distal splenorenal shunt. One patient in group B developed portal vein rupture due to infection. Biliary complications not associated with hepatic artery thrombosis were more common in group B, but the difference was not significant ($P = 0.4$).

The biochemical profile of the donors in the two groups was similar (mean ALT: 64.2 ± 22.2 vs 79.3 ± 2.1, mean prothrombin time 10.5 ± 0.9 vs 12.8 ± 0.4, respectively) except for the total bilirubin which was 1.7 + 0.5 (0.4–

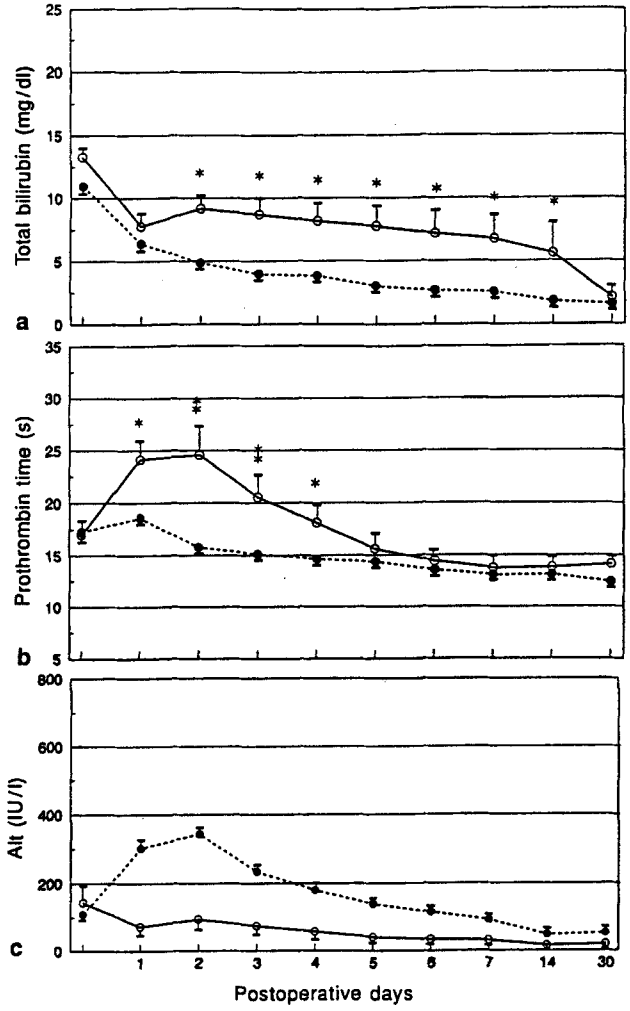

Fig. 2. **a** Serum total bilirubin, * $P < 0.05$. **b** Prothrombin time, * $P < 0.05$, ** $P < 0.01$. **c** ALT (alanine aminotransferase) in groups A1 and B1 (patients without complications).—o—Group A1, $n = 7$; —•— group B1, $n = 51$

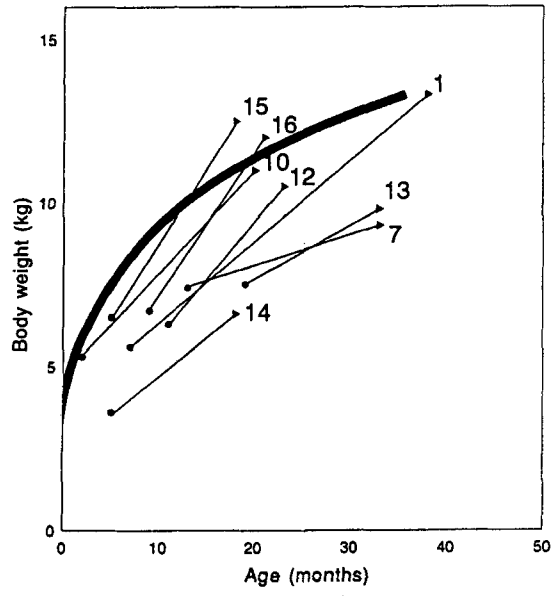

Fig. 3. Body weight changes in eight patients in group A who survived with their primary grafts during the observation period. *Dotted line* denotes 50th percentile body weight from the study of the National Center for Health Statistics Percentiles [5]

8.4) mg/dl in group A and 0.7 ± 0.1 (0.1–6.7) mg/dl in group B ($P < 0.05$).

Perioperative biochemical values were compared between groups A1 ($n = 7$) and B1 ($n = 51$, Fig. 2). Serum total bilirubin levels in days 1 through 14 and prothrombin time for days 1 through 4 were significantly higher in group A1. Serum ALT levels were not significantly different.

Eight of the patients in group A were alive with their primary grafts. The body weight at the time of transplantation was below the 5th percentile in six of them, at the 5th–10th percentile in one, and at the 25th–50th percentile in the eight patient. All patients gained weight during the observation period. While three patients remained at the 5th percentile, all others upgraded (Fig. 3).

Discussion

There are two features of neonatal liver transplantation requiring special consideration: technical difficulties due to the small size of the grafts [4], and functional performance, because neonatal livers are thought to be immature [3, 9, 11].

The increased incidence of hepatic artery thrombosis in the patients with neonatal transplants can be seen as a reflection of the technical difficulties encountered [10, 17, 21]. Interestingly, other complications related to the venous or biliary reconstructions did not occur with a greater frequency in the neonatal group. The possible role of immaturity of the graft and delayed function may also be related to hepatic artery thrombosis because of decreased or absent protein C synthesis by the newly transplanted liver [6].

Of the liver function tests referred to here, the prothrombin time is representative of the synthetic function of the liver and the total bilirubin of its ability to clear metabolic waste products. It appears that neonatal liver grafts gain normal synthetic function within 4–5 days after transplantation. Older donor grafts normally function immediately after transplantation. The ability to clear bilirubin is even more slowly regained: total bilirubin did not return to normal for 1 month, as compared to 1 week in grafts from older donors. Interestingly, after this slow recovery, which appears to be characteristic of the neonatal donor livers, the ultimate result is indistinguishable from that of livers from older donors.

Growth of the patients with liver grafts from neonatal donors appears to be similar to that observed previously in pediatric liver transplant recipients [15, 22].

In conclusion, if successful, neonatal liver transplantation can have equally good results as transplantation with livers from older donors.

Acknowledgements. Supported by research grants from the Veterans Administration and project grant no. DK 29961 from the National Institutes of Health, Bethesda, Md., USA.

References

1. Bismuth H, Houssin D (1984) Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 95: 367–370
2. Brolsch CE, Emond JC, Thistlethwaite JR, Whitington PF, Zucker AR, Baker AL, Aran PF, Rouch DA, Lichtor JL (1988) Liver transplantation, including the concept of reduced-size liver transplants in children. Ann Surg 208: 410–420
3. Buchanan GR (1978) Neonatal coagulation: normal physiology and pathophysiology. Clin Haematol 7: 85–109
4. Esquivel CO, Koneru B, Karrer F, Todo S, Iwatsuki S, Gordon RD, Makowka N, Marsh WJ, Starzl TE (1987) Liver transplantation before one year of age. J Pediatr 110: 545–548
5. Hamil PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM (1979) Physical growth: National Center for Health Statistics Percentiles. Am J Clin Nutr 32: 607–629
6. Harper PL, Edgar PF, Luddington RJ, Seaman MJ, Carrel RW, Salt AT, Barnes N, Rolles K, Calne RY (1988) Protein C deficiency and portal thrombosis in liver transplantation. Lancet II: 924–927
7. Kalayoglu M, Sollinger HW, Stratta RJ, D'Alessandro AM, Hoffmann RM, Pirsch JD, Belzer FO (1988) Extended preservation of the liver for clinical transplantation. Lancet I: 617–619
8. Kalayoglu M, D'Alessandro AM, Sollinger HW, Hoffman RM, Pirsch JD, Belzer FO (1990) Experience with reduced-size liver transplantation. Surg Gynecol Obstet 171: 139–147
9. Maisels MJ (1972) Bilirubin – on understanding and influencing its metabolism in the newborn infant. Pediatr Clin North Am 19: 447–501
10. Mazzaferro V, Esquivel CO, Makowka L, et al (1989) Hepatic artery thrombosis after pediatric liver transplantation: medical or surgical event? Transplantation 47: 971–977
11. Oski FA (ed) (1981) Neonatology. Lippincott, Philadelphia, pp 545–582
12. Otte JB, Ville de Goyet J de, Sokal E, Alberti D, Moulin D, Hemptinne B de, Veyckemans F, Van Obbergh L, Carlier M, Clapuyt PH, Claus D, Jamart J (1990) Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. Ann Surg 211: 146–157
13. Report of the medical consultants on the diagnosis of death to the president's commission for the study of ethical problems in medicine and biomedical and behavioral research (1981) Guidelines for the determination of death. JAMA 246: 2184–2186
14. Shaw BW, Martin DJ, Marquez JM, Kang YG, Bugbee AC, Iwatsuki I, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE (1984) Venous bypass in clinical liver transplantation. Ann Surg 200: 524–534
15. Spolidoro JPN, Berquist WE, Pehlivanoglu E, Saluski I, Vargas J, Ament ME (1988) Growth acceleration in children after orthotopic liver transplantation. J Pediatr 112: 41–44
16. Starzl TE (ed) (1969) Experience in hepatic transplantation. Saunders, Philadelphia, pp 1–545
17. Starzl TE, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli B, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT, Porter KA (1982) Evolution of liver transplantation. Hepatology 2: 614–636
18. Starzl TE, Iwatsuki S, Esquivel CO, Todo S, Kam I, Lynch S, Gordon RD (1985) Refinements in surgical technique of liver transplantation. Semin Liver Dis 5: 349–356
19. Teperman L, Podesta L, Mieles L, Starzl TE (1989) The successful use of older donors for liver transplantation. JAMA 262: 2838
20. Todo S, Fung JJ, Starzl TE, Tzakis A, Demetris AJ, Kormos R, Jain A, Alessiani M, Takaya S, Shapiro R (1990) Liver, kidney and thoracic organ transplantation under FK 506. Ann Surg 212: 295–307
21. Tzakis AG, Gordon RD, Shaw BW, Iwatsuki S, Starzl TE (1985) Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. Transplantation 40: 667–671
22. Urbach AH, Gartner JC Jr, Malatack JJ, Zitelli BJ, Iwatsuki S, Shaw BW, Starzl TE (1987) Linear growth following pediatric liver transplantation. Am J Dis Child 141: 547–549
23. Zitelli BJ, Malatack JJ, Gartner JC, Urbach AH, Williams L, Miller JW, Kirkpatrick B (1987) Evaluation of the pediatric patient for liver transplantation. Pediatrics 78: 559–565