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Regeneration of Graft Liver in Adult-to-adult Living Donor Liver Transplantation using a Left Lobe Graft

Graft size-matching is one of the critical concerns in adult-to-adult living donor liver transplantation (ATALDLT). In this study, we evaluated regeneration of a small-for-size graft less than 50% of the standard liver volume (SLV). We reviewed nine patients of united network of organ sharing (UNOS) status 2 or 3 who had undergone ATALDLT with a left lobe graft. For the comparison of liver regeneration, 20 hepatectomized patients for biliary malignancy were selected as non-transplant control group. In the ATALDLT group, graft size ranged from 30 to 49% of the SLV of recipients and their regeneration rates were 158%, 182%, 200% and 185% after 1, 2, 3 and 4 weeks following transplantation, respectively. In the control group, preoperative volume of left lobe to whole liver volume ranged between 40 and 54% and their regeneration rates were 145%, 156%, 163% and 177% after 1, 2, 3 and 4 weeks following extended right lobectomy, respectively. There was no statistical difference in regeneration rates between two groups. In the ATALDLT group, serum aspartate aminotransferase showed the median peak level of 198 IU/L on the first postoperative day and it was normalized within one week. Recovery of bilirubin clearance lagged behind rapid volume regeneration by about one week. Two patients died of sepsis. We postulate that the regenerative power of small-for-size grafts from living donors is preserved, although time-lag between volume regeneration and metabolic capability occurs in small-for-size grafts, when the initial graft volume meets metabolic demands during the early postoperative days.

Key Words : *Liver transplantation, living donor; Liver regeneration; Small-for-size graft; Graft size-matching*

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INTRODUCTION

Shortage of cadaveric donor livers led to the emergence of living-donor liver transplantation (LDLT). Initially it was developed for pediatric patients because of the scarcity of pediatric cadaveric donors (1). Furthermore, a desperate lack of adult cadaveric donors forced its extension to adult patients as well (2, 3).

The difference of LDLT from cadaveric donor liver transplantation (CDLT) initiates in the orders of selecting a recipient and a donor in which the recipient seeks proper living donor. Selection of living donor is mainly based on lobar volumes and vascular anatomy of the liver. Preoperative evaluation of graft size is an essential process in LDLT since proportion of lobar volume to whole liver volume is variable. Graft size-matching for adult-to-child LDLT is not difficult in most cases because most of the parents can afford sufficient volume of graft for the relatively small body size of pediatric recipients. However, most grafts procured from living donors through left lobectomy or even through right lobectomy are small-for-size in adult-to-adult living donor liver transplantation (ATALDLT), in which proper graft size-matching is critical for a successful outcome. Too small a graft may lead to hepatic failure, whereas large graft procurement can threaten the safety of living donor.

The liver has a vigorous regenerating capability when it is resected. This unique capability may allow the ATALDLT recipients with small-for-size grafts survive. Regeneration of hepatectomized livers has been well documented (4, 5), but that of small-for-size transplant grafts has been rarely analyzed (6, 7). The regenerating power of graft liver may play a pivotal role in the clinical course of ATALDLT and adequacy of graft size-matching should be determined on the basis of liver regeneration. It is also postulated that metabolic demand from the

pretransplant condition of recipients and preservation-reperfusion injury can affect the regenerating power of small-for-size graft liver.

In this study, we evaluated regeneration of small-for-size grafts of less than 50% of the standard liver volume (SLV) by comparing regeneration rates of graft volumes following ATALDLT with non-transplant hepatectomized livers and by analyzing the posttransplant recovery course.

MATERIALS AND METHODS

We analyzed nine cases of ATALDLT with a left lobe graft performed at Asan Medical Center from February 1997 to October 1997. The profiles of recipients and donors are summarized in Table 1. Preoperative general condition of all recipients was united network of organ sharing (UNOS) status 2 or 3.

Hepatectomies for donor and recipient were performed concurrently. Extended left lobectomy of the donor was done without interruption of hepatic inflow. As soon as completion of in situ perfusion of graft with HTK solution, the graft was delivered to the recipient and vascular reconstruction of the graft began consecutively. Portal blood flow was resumed immediately after hepatic vein anastomosis with a piggy back method and anastomosis of the portal vein. Hepatic artery reconstruction was performed by microscopic surgical technique. Roux-en Y hepaticojejunostomy was followed as a biliary reconstruction. Follow-up volumetric computed tomogram (CT) scans have been performed prospectively at 1, 2, 3 and 4 weeks after ATALDLT in 8 cases.

For comparison of regeneration power of livers, we selected 20 patients who had undergone extended right lobectomy and bile duct resection for biliary malignancy as a non-transplant control group. Their diagnoses were hilar bile duct cancer in 15 cases and advanced gallbladder cancer in 5 cases. Ages ranged from 40 to 66 years and male-to-female ratio was 13:7. Thirteen patients out of 20 had undergone preoperative right portal vein embolization (PRPVE) to induce compensatory hypertrophy of left lobe (8). They had also undergone prolonged biliary decompression when obstructive jaundice had been combined. They underwent postoperative CT scans at least once within one month of hepatectomy. Liver volume was measured retrospectively using CT volumetry.

The regeneration rate of graft liver was calculated as follows; "(postoperative volume of graft (ml)/graft weight (g)) $\times$ 100%". In the control group, liver regeneration rate was calculated as "(postoperative remnant liver volume (ml)/preoperative left lobe volume (ml)) $\times$ 100%". Liver volume at 2 weeks after PRPVE was adopted when PRPVE was performed.

We used the formula of SLV for Korean adults, "SLV (ml) = 691 $\times$ body surface area (m^2) + 95", which we have reported elsewhere (9). Degree of graft size-matching was expressed as percentage of graft weight (g) to SLV (ml), where Heymsfield et al. (10) had reported that liver volume measured by CT volumetry and real liver weight are interchangeable since density of the liver is equivalent to that of water.

Serum total bilirubin level was used for evaluation of metabolic capability of the graft. Serum aspartate aminotransferase (AST) was used to evaluate the parenchymal injury to the graft associated with preservation and reperfusion.

The values are expressed as median. Median test (Statistica 5.0, U.S.A.) was used for comparison of regeneration rates and a p value less than 0.05 was regarded as statistically significant.

RESULTS

In the ATALDLT group, graft size ranged from 30

Table 1. Profile of recipients and donors who underwent adult-to-adult living donor liver transplantation using a left lobe graft

Recipient			Relation	Donor		Graft		Outcome
Disease	Sex/Age	BW (kg)		Sex/Age	BW (kg)	Weight (g)	%SLV	
HCC, Hepatitis B	M/38	60	third cousin	M/39	76	550	48%	good
Hepatitis B	M/39	63	brother	M/23	64	375	30%	good
Hepatitis B	F/58	38	sister-in-law	F/46	83	480	49%	fail
Hepatitis B	M/49	58	(−)	M/30	89	420	37%	good
Alcoholic LC	M/51	73	nephew to uncle	M/29	80	575	43%	fail
Hepatitis B	M/32	50	marriage in-law	M/33	65	450	40%	good
HCC, Hepatitis B	M/52	59	son to father	M/20	76	625	49%	good
HCC, Hepatitis B	M/54	74	(−)	M.30	73	570	42%	good
HCC, Hepatitis B	F/35	54	husband to wife	M/40	76	525	45%	good

BW, body weight; %SLV, percentage of standard liver volume; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

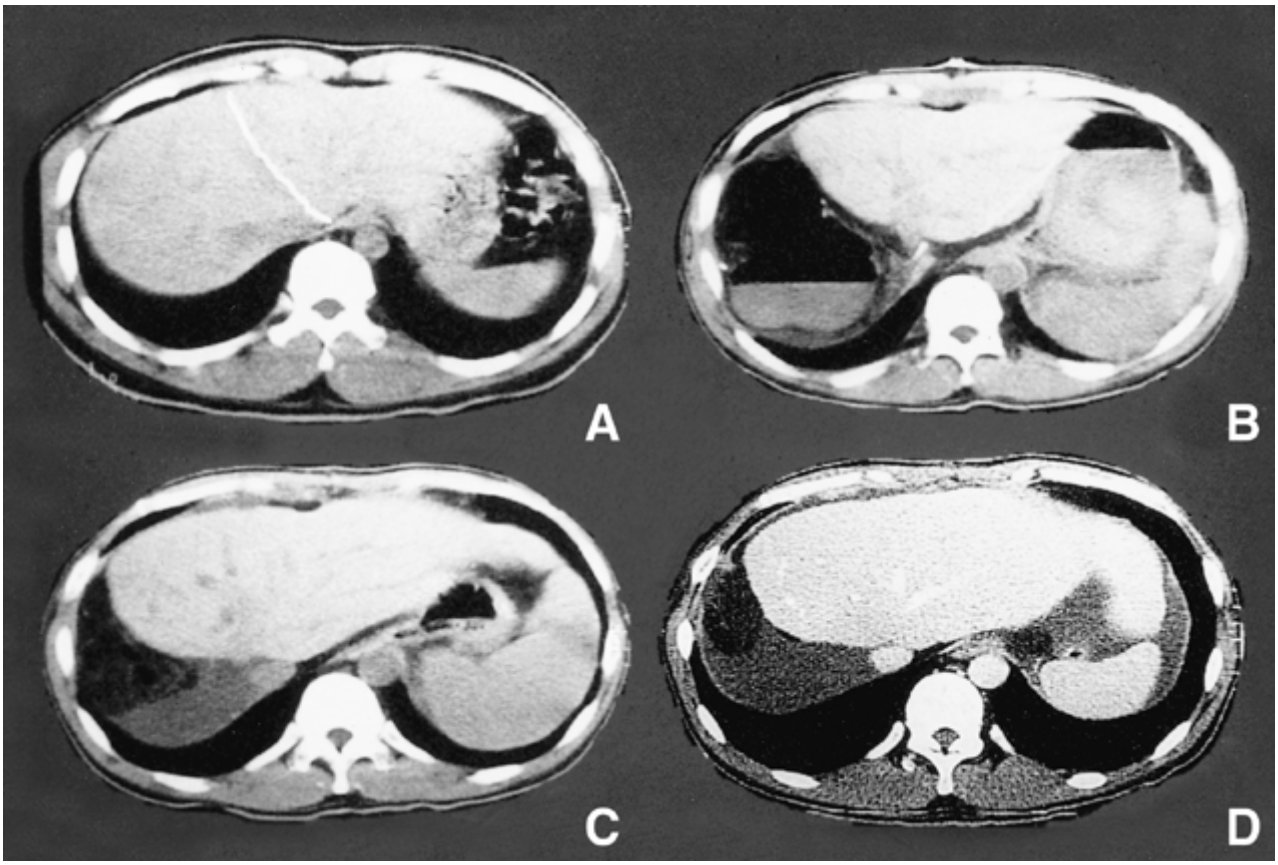

Fig. 1. Computed tomographic scans of donor and recipient after adult-to-adult living donor liver transplantation. A) Donor's liver, 375 g of left lobe graft; B) 587 ml liver volume 1 week after transplantation; C) 818 ml liver volume 3 weeks after transplantation; D) 923 ml liver volume 2 months after transplantation.

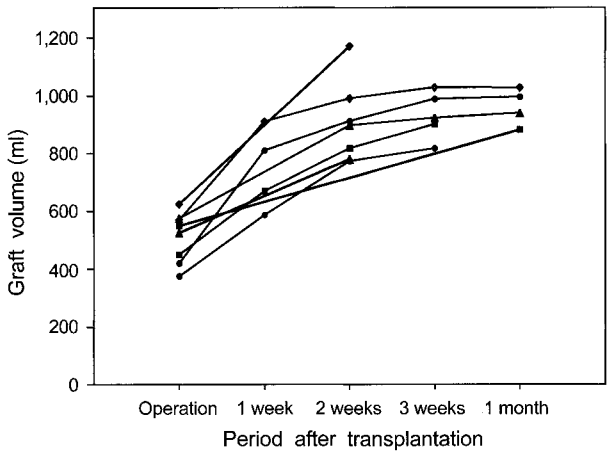

Fig. 2. Volume regeneration of graft liver measured by computed tomographic volumetry following adult-to-adult living donor liver transplantation using a left lobe graft. Graft weight (g) measured at operation was regarded as equivalent to graft volume (ml).

to 49% of SLV of recipients. Sequential volume changes of grafts are shown in Fig. 1 and Fig. 2. Regeneration rates were 158%, 182%, 200% and 185% after 1, 2, 3 and 4 weeks following ATALDLT, respectively. In the non-transplant control group, preoperative volume of left lobe to whole liver volume ranged 40 to 54% and regeneration rates were 145%, 156%, 163% and 177% after 1, 2, 3 and 4 weeks following extended right lobectomy, respectively (Fig. 3). There was no statistical difference in regeneration rates between the two groups at corresponding postoperative periods ($p>0.05$).

In the ATALDLT group, serum AST showed a peak level of 198 IU/L on the first postoperative day, and dropped to 40 IU/L by the seventh day. Thereafter, it was normalized (Fig. 4). Serum total bilirubin reached up to 7.4 mg/dL during the first week, and dropped to 3.5 mg/dL at the end of the second week (Fig. 5).

Two recipients died of sepsis on the 21st and 40th postoperative day. Hepatic failure due to inadequate graft volume did not contribute to patient death.

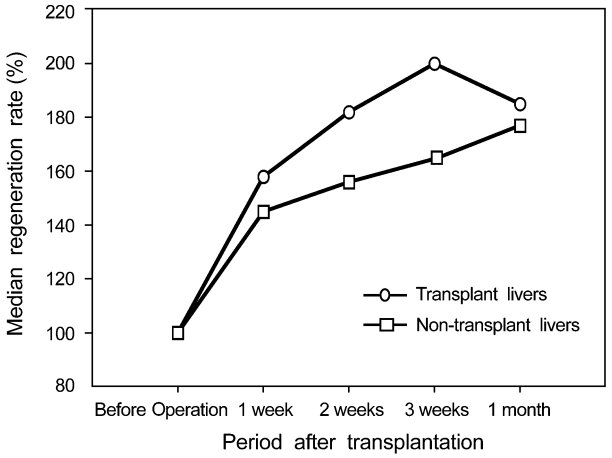

Fig. 3. Comparison of regeneration rates of graft volumes following adult-to-adult living donor liver transplantation using a left lobe graft (*transplant livers*) and remnant liver volumes following extended right lobectomy (*non-transplant livers*). In transplant livers, baseline volume was the value converted directly from graft weight, whereas left lobe volume was used in non-transplant livers. All values are expressed as median. Unusual drop of regeneration rate at 4th week in transplant livers was resulted from different samples of liver volume, which were shown in Fig. 2 and did not mean the decrease of liver volume.

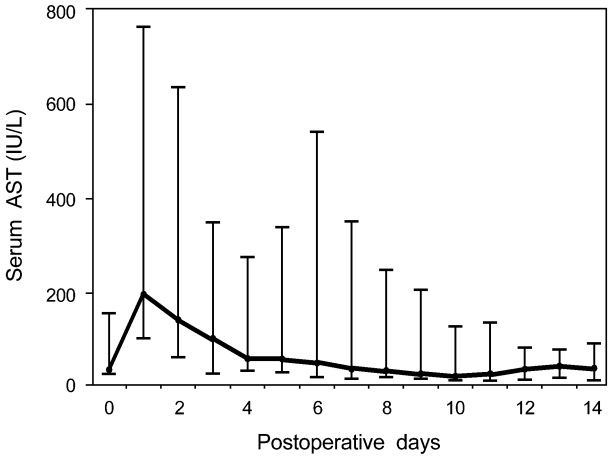

Fig. 4. Trends of changes in serum aspartate aminotransferase following adult-to-adult living donor liver transplantation using a left lobe graft. Thick line indicates median. Ranges of maximal and minimal values are plotted in the form of whiskers.

DISCUSSION

The regenerating capability of non-transplant hepatectomized livers is known to be presented in various degrees according to the extent of resection and functional reserve (4, 5). The more extensively a liver is resected, the more rapidly liver regeneration may occur. This rule of thumb is often observed during the follow-up of hepatectomized patients. Our early experience postulated that small-for-size transplant liver may follow that rule.

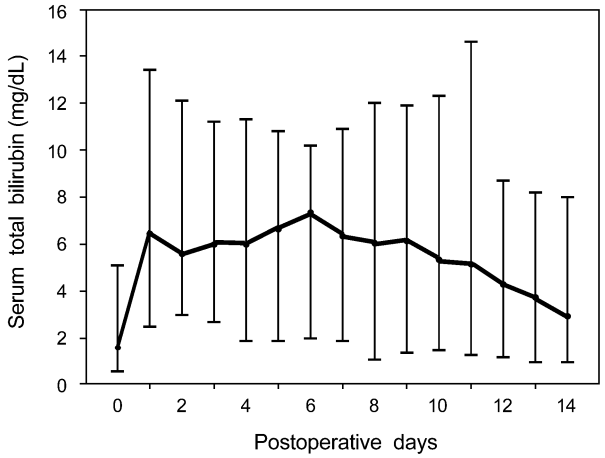

Fig. 5. Trends of changes in serum total bilirubin following adult-to-adult living donor liver transplantation using a left lobe graft. Thick line indicates median. Ranges of maximal and minimal values are plotted in the form of whiskers.

In our series, small-for-size grafts of less than 50% of SLV from left lobectomy regenerated well, as much as the non-transplant livers did. Although transplant livers seemed to grow at more accelerated rates than non-transplant livers (Fig. 2), this difference might originate from different calculation methods in measuring baseline left lobe volume and different extents of liver resections. In the ATALDLT group, weight of left lobe parenchyme was measured directly and converted to volume by way of water density. However, in the non-transplant control group, CT volumetry was used for the measurement of preoperative left lobe volume, of which PRPVE had already induced compensatory hypertrophy in 13 cases and extents of liver resection larger than right lobectomy were ignored. Median volume of graft to SLV was 43%, whereas median remnant liver volume to original whole liver was 46%. Even without consideration of these discrepancies, rates of volume regeneration in the two groups did not show any significant differences. This indicates that small-for-size transplant livers have similar regenerating powers to non-transplant hepatectomized livers.

One of the morphologic characteristics observed in regenerated grafts was markedly dilated intrahepatic portal vein and its branches according to expansion of surrounding parenchyme (Fig. 1B, 1C). Meanwhile, hepatic vein and intrahepatic bile ducts seemed to remain unchanged or be dilated slightly (Fig. 1D). We also noted that the size of the intrahepatic portal vein measured by

Doppler-ultrasonography, which was performed regularly, was well correlated with the volume expansion of graft measured by CT volumetry. Therefore, graft regeneration can be predicted by portable ultrasonography when a recipient's status does not permit moving to the CT room.

The pretransplant condition of recipients were UNOS status 2 or 3 in this study. In LDLT, parenchymal injury associated with preservation and reperfusion is known to be less severe than in CDLT (2, 11). Cold ischemic time was usually less than one hour in our series, which might result in minimal preservation injury and good viability, since graft procurement was performed concurrent with the recipient operation. Preservation-reperfusion injury in the ATALDLT group might be compatible with parenchymal injury from obstructive jaundice and surgical procedures using temporary interruption of hepatic blood inflow in the control group because their pattern of changes in serum aminotransferase levels was similar each other.

Delayed recovery of bilirubin clearance is one of the characteristics of small-for-size grafts (2, 3, 11). Volume regeneration of graft occurred most vigorously during the first week when serum total bilirubin reached at an elevated level. At the end of second week, metabolic capability seemed to be restored as serum bilirubin level was decreasing with slowdown of volume regeneration. This time-lag between volume regeneration and metabolic capability might have been contributed to by relatively small size of graft liver to metabolic demand from the recipient.

The result of this study proposes that small-for-size graft of ATALDLT in the range of 30 to 49% of SLV may have similar regenerating capability to non-transplant hepatectomy of corresponding extents. Conversely, once the small graft can meet the metabolic demand in the early postoperative period, the graft liver may grow rapidly until there is sufficient regeneration. It also indicates that degree of metabolic demand should be considered in determining adequacy of graft size-matching. Makuuchi et al. (7, 12, 13) proposed that a graft size of more than 30% of the SLV for metabolic diseases and more than 40% of SLV for cholestatic diseases should be afforded for successful LDLT.

Conclusively, it is suggested that the regenerating power of graft livers from living donors is well preserved, although time-lag between morphologic regeneration and metabolic capability occurs in small-for-size graft, so that the minimal requirement of graft volume for successful ATALDLT is at least equivalent to the liver volume needed to meet metabolic demands during early postoperative days.

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