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Reduction of left-lateral segment from living donors for liver transplantation in infants weighing less than 7 kg: technical aspects and outcome

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Running title: Reduction of left-lateral segment graft

Key words: living donor liver transplantation, monosegment, large-for-size graft, primary closure

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Abbreviations: LDLT, living donor liver transplantation; LLS, left-lateral segment;
RLLS, reduced left-lateral segment; GRWR, graft-to-recipient weight ratio; CT, computed tomography.
Abstract

Background. Left-lateral segment (LLS) reduction has been frequently used in infants weighing less than 7 kg.

Patients and methods. Twenty recipients weighing less than 7 kg at the time of living donor liver transplantation (LDLT), median age 11.0 months and body weight 5.6 kg, were treated with a reduced left-lateral segment (RLLS) (n = 12) or LLS (n = 8) graft. Absolute indication for size reduction was that the estimated graft-to-recipient weight ratio (GRWR) was >4.0%. Even if the preoperative GRWR was <4.0%, the RLLS graft was considered to ensure a size match. A flatfish-type LLS was preferred to a blowfish-type to make a RLLS graft for such a small infantile population.

Results. The RLLS recipients had significantly more flatfish-type grafts, while the LLS recipients had more blowfish-type grafts. Primary full-layer wound closure could be performed successfully in all LLS recipients, while in the RLLS group, two patients were forced to have partial skin closure. There were no graft losses related with graft compression.

Conclusion. Reducing a LLS is a useful procedure to promote the comfortable accommodation of the graft in an infant weighing less than 7 kg. Flatfish-type LLS allowed more flexibility to make the suitable volume.
**Introduction**

A shortage of size-mismatched donors for pediatric recipients has led to the development of reduced, split and living-donor liver transplantation (LDLT) (1, 2). In these techniques, to overcome size discrepancies between adult donors and pediatric recipients, the left-lateral segment (LLS) is used as the liver graft. However, even these grafts may be too large for small infants.

Large-for-size grafts are encountered in neonatal or infant liver transplantation. The main problems are the small size of the recipient’s abdominal cavity and the inability to provide an adequate blood supply to the graft (3). The technique of LLS reduction has been developed recently to address these problems and applied to infant recipients, especially those weighing less than 7 kg (4–8). The initial indication for using a reduced left-lateral segment (RLLS) graft was an estimated graft-to-recipient weight ratio (GRWR) of >4.0%, as assessed by preoperative computed tomography (CT) volumetry (9). However, not only the GRWR, but also the shape of the LLS of the donor should be considered, to make abdominal closure easier.

We retrospectively reviewed the operative characteristics of 20 infant recipients weighing less than 7 kg who underwent LDLT in our institute. Special attention was paid to our procedure to reduce the LLS and the outcome of the LDLT with the RLLS compared to with the LLS graft.
Patients and methods

Patients

Between September 2000 and January 2009, 62 pediatric patients (less than 15 years old) underwent 63 LDLTs at Kumamoto University Hospital. Twenty of these pediatric recipients (32.3%) weighed less than 7 kg at the time of LDLT, and a RLLS graft was considered. Median age and weight were 11.0 months (range: 2–18 months) and 5.6 kg (range: 3.2–7.0 kg), respectively. Eight of the 20 infants were male, and the underlying diseases were 12 cases of biliary atresia, four of fulminant hepatic failure, and one each of Alagille syndrome, cryptogenic liver cirrhosis, hepatoblastoma and mitochondrial DNA depletion syndrome. The patients were followed up until March 2009 for a median period of 27.0 months (range: 0.0–86.0 months). Potential donors were evaluated by liver function tests, identification of anatomical variations, and graft size. The hepatic anatomy was examined using both preoperative three-dimensional CT and ultrasonography. All patients received grafts from either their mothers or fathers.

In principle, the LLS was used as the graft unless the GRWR of the whole LLS estimated by preoperative CT volumetry was >4.0%. The shape of the LLS was evaluated by preoperative CT and classified into a blowfish type with a short and thick shape, and a flatfish type with a flat and long shape (Fig. 1), as described previously.
(10). We have accepted all potential donors regardless of the estimated GRWR and the shape of the LLS, although we prefer a flatfish-type LLS to a blowfish-type as a graft for such a small infantile population because the latter is technically difficult to reduce the volume. Additionally, even if the preoperative GRWR was <4.0%, the RLLS graft was considered, in order to ensure a size match between the abdominal cavity and the graft. The medical records of 20 patients weighing less than 7 kg who underwent LDLT were reviewed, and the perioperative characteristics between the patients treated with a LLS or a RLLS graft were compared.

**Operations**

In the donor, after isolation of the left hepatic pedicle, the hepatic parenchyma was transected, following a cutting line 5 mm to the right side of the falciform ligament, using an ultrasonic dissector and bipolar electrical cautery without inflow occlusion. In cases of reduction, the lateral part of the LLS was resected while preserving the medial branches of the left hepatic vein. After the resected part was weighed, additional resection of the caudal part, without ligation of any branches to segment III, was considered. If needed, the dorsal part was also resected, leaving the proximal part of the portal branch to segment II intact (Fig. 2). The graft liver was removed after vascular clamping, followed by *in situ* perfusion through the left portal vein with University of Wisconsin solution (ViaSpan; Bristol-Myers Squibb Co., New York, NY) or
histidine/tryptophan/ketoglutarate solution (Custodiol; Odyssey Pharmaceuticals, Inc., East Hanover, NJ).

In the recipient, the liver graft was implanted in an orthotopic manner after total hepatectomy, while preserving the inferior vena cava. The graft liver was reperfused following completion of portal venous reconstruction. The hepatic artery was then anastomosed using a microsurgical technique. The biliary tract was reconstructed by duct-to-duct anastomosis, except in recipients with biliary atresia in principle (11). The abdominal wound was carefully closed under monitoring of hepatic venous and portal blood flow by Doppler ultrasonography.

Immunosuppression

Immunosuppression consisted of tacrolimus and low-dose steroids. Target trough level of tacrolimus was 12–15 ng/ml for the first 2 weeks, 10–12 ng/ml for the next 2 weeks, and 5–10 ng/ml thereafter. Steroid treatment was initiated with an injection of 10 mg/kg methylprednisolone prior to graft reperfusion during surgery, and it was usually tapered off until complete withdrawal around 3–6 months after transplantation.

Statistical analysis

Data were expressed as means ± SD. Fisher’s exact test, unpaired t test and log-rank test were used for statistical analysis. p < 0.05 was regarded as significant.
Results

The profiles of RLLS and LLS graft donors did not differ significantly (Table 1). The reduction procedure had no disadvantages for the donor. Comparison between the recipients treated with RLLS and LLS grafts is shown in Table 2. The estimated GRWR was significantly larger in those receiving a RLLS graft, when it was calculated with the weight of the original (non-reduced) LLS. There was no significant difference in the GRWR between the RLLS and LLS graft recipients, when calculated with the actual graft weight after reduction. Volume reduction of the LLS significantly reduced the graft weight and GRWR from $256.9 \pm 62.4$ to $193.7 \pm 40.4$ g and from $4.97 \pm 1.72$ to $3.63 \pm 0.75 \%$, respectively ($p < 0.05$). Although preoperative CT images were available in only 17 cases, the recipients with a RLLS graft had significantly more flatfish-type grafts, while those with a LLS graft had more blowfish-type grafts ($p < 0.05$). Primary full-layer wound closure could be successfully carried out in all LLS graft recipients, while two recipients with a RLLS graft were forced to have partial skin closure ($p > 0.05$).

All 20 transplantations were of single anastomosis to reconstruct hepatic vein although venoplasty to create a single orifice on graft was needed in 3 of 12 RLLS grafts and in 3 of 8 LLS grafts ($p > 0.05$). The interposition grafts for portal venous
reconstruction were employed in 2 of 12 RLLS grafts and in 4 of 8 LLS grafts (p > 0.05). All 20 recipients had single anastomosis with no interposition grafts for hepatic artery reconstruction. Duct-to-duct choledochocholedochostomies were carried out in recipients with the intact extrahepatic biliary tract even though they were very small infants (11). There were no grafts accompanied with multiple bile ducts, and the 12 patients treated with RLLS grafts had the 6 Roux-en-Y hepaticojejunostomies and 6 duct-to-duct choledochocholedochostomies, whereas all the 8 with LLS grafts were treated with hepaticojejunostomy (p < 0.05). There were three episodes of surgical complications (15.0%) and four of vascular complications (20.0%). The incidence of these complications was not significantly different between the two groups (Table 3). No early vascular complications related to graft compression developed in either group.

The reduction procedure and clinical outcome of 12 patients treated with a RLLS graft are summarized in Table 4. Three patients had three resected pieces of LLS, five patients had two pieces, and four patients had one piece (Fig. 2). The blowfish-type grafts had more resected pieces than the flatfish-type probably showing insufficient volume reduction in the former although the difference was not significant (2.7 ± 1.2 versus 1.9 ± 0.9, p > 0.05). The GRWR for LLS in Case 5, 6, 7, 9 and 12 had been estimated to be <4.0%. Case 9 underwent LDLT with a LLS graft with the GRWR of 3.62% first, but reperfusion following successful anastomosis led to severe hypoperfusion in a lateral part of the graft. The portion was immediately resected with
no inflow occlusion because it seemed to develop massive necrosis. In the other 4 cases, a RLLS graft was employed to accommodate the graft comfortably with no compression in their small abdominal cavities in spite of the estimated GRWR <4.0%. In Case 1 and 10 with non-chronic liver disease, it was necessary to close the abdominal wall with partial skin closure. Although complications developed in three patients, they did not lead to any graft losses. Leakage of hepaticojejunostomy in Case 2 developed on postoperative day 14, and Case 8 had outflow block 6 months after LDLT. These complications were treated successfully with surgical revision and percutaneous transhepatic balloon dilation, respectively. Portal vein thrombosis developed 6 months after transplantation in Case 5, and unfortunately, radiological intervention ended in failure. The patient has maintained a patent intrahepatic portal vein through the cavernous transformation and liver function has been stable with no clinical manifestation of portal hypertension. Five patients have been dead during the follow-up period. The one died from the progression of heart failure immediately after surgery, whereas the other four died from causes unrelated to surgical procedures, including malignancy.
Discussion

The Japanese law on organ transplantation still bans organ donation from children younger than 15 years old. Consequently, a size matched child donor cannot be obtained as donor, but a partial liver transplant is necessary, either from a live or a deceased donor. In Japan, the technique to reduce a part of the LLS \textit{in situ} was first introduced at Kyoto University Hospital in September 2000. There is no doubt that this expanded the donor pool for LDLT in small babies with liver failure and made it safer (9). This technique was further developed to make the grafts more suitable for neonates and extremely small babies. Recently, the procedure to resect a caudal part in addition to a lateral part of the liver was introduced (12). The liver weight constitutes 4–5% of body weight at birth. Considering the average weight of the LLS graft, reduction in graft size should be considered in recipients weighing less than 7 kg (8).

A major concern during reduction of the LLS is injury of the proximal portal and hepatic veins, although the distal hepatic vein that drains segment II must be ligated when a lateral part of the LLS is resected. The step-by-step volume reduction of a LLS is a safe procedure that has no disadvantages for the donor. The disadvantage of large-for-size graft is considered the insufficient tissue oxygenation, which would be further compounded by compression of the graft and vessels in the abdominal closure (3, 9, 13). We had a patient treated with the large GRWR of $>5.0\%$ in the early days.
Fortunately, the patient showed neither graft hypoperfusion nor immediate severe graft dysfunction.

A higher incidence rate of surgical complications, including vascular disorders, has been reported in infants treated with a RLLS graft (9). Although liver transplantation in small infants provides similar results as that in older patients, it is still more challenging technically, because of the smaller vascular structures. Consequently, there is no doubt that small infants who are undergoing LDLT have an increased risk of surgical complications, such as vascular stricture or thrombosis (14, 15). The incidence of hepatic vein, portal vein and hepatic artery complications has been reported as 1.5–4%, 1.2–16.5% and 7–10%, respectively, in pediatric liver transplant programs (16–21). In the present study, there was no significant difference in the incidence of surgical complications, including vascular disorders, between the RLLS and LLS graft recipients, and the incidence of hepatic vein, portal vein and hepatic artery complications was 10, 10 and 0%, respectively. In other words, LLS reduction seemed to have no impact on the incidence of surgical complications. However, we unfortunately lost five infants during the study period, suggesting the difficulty of applying liver transplantation that is a mere local treatment to probably systemic diseases in such a small infantile population.

The LLS is diverse in terms of shape and volume. In the present study, the weight of the LLS ranged from 165 to 395 g. The LLS can be classified according to the blowfish
type and the flatfish type (10). Our major objective when reducing LLS graft size is to accommodate the graft comfortably with no compression in a very small abdominal cavity, in addition to producing a GRWR of <4.0%. Consequently, most of the RLLS grafts were the flatfish type, while most of the LLS grafts were the blowfish type in our institute. And then, primary full-layer wound closure was feasible in most RLLS graft recipients and in all LLS graft recipients. A lateral portion of a flatfish-type LLS should be removed to allow more comfortable graft accommodation in the small abdominal cavity, even if the estimated GRWR of the LLS graft is <4.0%. In the present study, all 12 recipients had primary abdominal closure, although two were forced to undergo partial skin suturing. The latter two recipients were extremely small and had non-chronic liver disease with no massive ascites. Previous studies with no RLLS grafts reported the frequent employment of silastic prosthesis to close abdominal wound with the acceptable outcomes in small infants (22, 23). Delayed primary closure of abdominal wall with temporary silastic patch has been reported to be a safe and useful technique (24, 25). However, we don’t accept the employment of prostheses because they may invite infectious complications (26). Ogawa et al. have reported that six of nine recipients treated with a RLLS graft were forced to undergo partial skin closure, to avoid compression injury of the graft and respiratory failure (12). Enne et al. have suggested that the major concern of transplantation with a RLLS graft is not the possibility of achieving primary abdominal-wall closure, but rather a sufficient vascular
inflow and tissue oxygenation in patients with a GRWR of >4.0% (7). However, our results suggest that reducing the size of the LLS promotes primary abdominal-wall closure. Conversely, if the LLS is a blowfish type with a GRWR of <4.0%, small infants seem to accommodate the graft comfortably. On the other hand, reducing a blowfish-type LLS is more technically difficult in spite of a limited effect to decrease the graft volume.

In conclusion, both flatfish-type and blowfish-type LLS are a valuable graft source with or without surgical reduction for LDLT in an infant weighing less than 7 kg, that can bring an acceptable surgical outcomes, although the latter more often needs partial abdominal closure. Even though GRWR of the original LLS is over 4 %, if it is flatfish-type, it is easy to make it less than 4% by reduction and to promote the comfortable accommodation in the recipient’s abdominal cavity. When the LLS is the blowfish-type, if the GRWR is less than 4%, it is also easy to accept it without reduction in this patient population.
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Figure legends

Fig. 1. LLS shape is classified into two types by preoperative CT: (A) blowfish type with a short and thick shape; and (B) flatfish type with a flat and long shape.

Fig. 2. Cutting lines to reduce a LLS. (1) The lateral part of the LLS is resected first, while preserving the medial branch of the left hepatic vein. (2) After the resected part is weighed, further reduction of the caudal part is performed, without ligation of any portal branches to segment III. (3) The additional resection of the dorsal part is carried out while the portal branch to segment II remains intact.