ELSEVIER

Experience With Recipient's Superficial Femoral Vein as Conduit for Middle Hepatic Vein Reconstruction in a Right-Lobe Living Donor Liver Transplant Procedure

K. Sato, S. Sekiguchi, T. Fukumori, N. Kawagishi, Y. Akamastu, Y. Enomoto, T. Iwane, K. Fujimori, A. Sato, and S. Satomi

ABSTRACT

Middle hepatic vein reconstruction during the right-lobe living donor liver transplant procedure has been recognized to be a significant factor. We initially reconstructed only a single middle hepatic vein orifice draining into segment 8. In cases where the right-lobe liver graft has several major middle hepatic vein tributaries, including veins draining segment 5 that are remote from the right hepatic vein orifice, a long and thick interposition conduit is necessary for reconstruction. Among 11 consecutive adult patients who received a right-lobe liver graft without a middle hepatic vein at our institution, 8 underwent reconstruction of all major middle hepatic vein tributaries using a vein graft from the recipient's superficial femoral vein. The remaining 3 patients had no major middle hepatic vein tributaries. Posttransplant-computed tomography imagings showed increased liver mass with a patent superficial femoral vein graft in 8 patients. In the absence of a venous system from a deceased donor, a recipient superficial femoral vein offers an excellent size match to maintain the venous outflow of middle hepatic vein tributaries. Reconstruction with recipient superficial femoral vein plays an important role in maximizing liver function and minimizing morbidity in the early posttransplant period.

LIVING donor liver transplantation (LDLT) using a right-lobe liver graft (RLG) is now the standard option for patients with end-stage liver disease. In contrast to an extended right-lobe liver graft including the trunk of the middle hepatic vein (MHV),[1] however, RLG without an MHV trunk can cause serious problems for the recipient owing to congestion in segments 5 and 8. The need for reconstruction of MHV tributaries has been a matter of controversy among transplant surgeons.[2–5]

Various vein grafts and technical modifications have been introduced to reconstruct MHV tributaries.[2–3,5–8] Among a variety of autologous vein grafts, the great saphenous vein (GSV) is commonly utilized for such reconstructive procedures. However, the superficial femoral vein (SFV) is preferable to a GSV graft in terms of caliber and wall thickness.[9] In our series, we decided to use the recipient's SFV as an interposition vein graft for reconstruction of MHV tributaries. We describe our experience with MHV reconstruction using the recipient's SFV in RLG without an MHV trunk.

PATIENTS AND METHODS

Between April 2003 and March 2004, 11 consecutive LDLT procedures using RLG were performed preserving the main MHV trunk that drained the remnant left-lobe liver in the donor. The 11 patients included 5 men and 6 women (mean age, 46 years; range, 32–59 years). Of the 11 RLGs, 8 had major MHV tributaries that exceeded 5 mm in diameter. There were no major MHV tributaries in the remaining 3 cases. The 11 total patients were divided into two groups according to presence of major branches of the MHV draining segments 5 and 8: group 1, a RLG with MHV reconstruction using recipient SFV (n = 8) and group 2, a RLG without MHV reconstruction due to absence of major MHV tributaries (n = 3). The indications for LDLT in this series of patients included fulminant hepatic failure (n = 4), primary biliary cirrhosis (n = 3), hepatitis B virus with cirrhosis (n = 1), adult-onset citrullinemia (n = 1), Caroli's disease (n = 1), and primary sclerosing cholangitis (n = 1). The donors consisted of a child (n = 3), spouse (n = 3), sibling (n = 2), parent (n = 1), or other relative (n = 2).

From the Department of Surgery, Graduate School of Medicine, University of Tohoku, Sendai, Japan.

Address reprint requests to Kazushige Sato, MD, Advanced Surgical Science and Technology Division, Department of Surgery, Graduate School of Medicine, University of Tohoku, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574, Japan. E-mail: satokazu@mail.tains.tohoku.ac.jp

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Table 1. Anatomic Variations of Venous Drainage and Estimated Graft Volume in 11 Right-Lobe Grafts

		Size	Number of Reconstructions		GV/SLV (%)	
	Case	RHV (mm)	I(M) RHV	MHV Tributaries	0	4 Weeks
Group 1 (n = 8)	1	27	0	2	56.4	96.0
	2	28	0	2	42.1	107.7
	4	29	1	2	52.9	86.9
	5	22	1	2	64.9	91.0
	6	25	0	3	58.7	92.8
	7	23	1	2	52.1	94.9
	9	17	2	2	56.7	99.8
	10	27	1	2	47.0	114.7
Group 2 (n = 3)	3	38	0	0	59.8	91.2
	8	25	0	0	47.7	65.6
	11	27	1	0	58.5	85.7

Abbreviations: RHV, right hepatic vein; I(M) RHV, inferior (middle) right hepatic vein; MHV, middle hepatic vein; GV/SLV, ratio of graft volume to recipient standard liver volume.

Donor Operation

In brief, the donor hepatic parenchyma in all cases was transected along the Cantlie line 1 cm to the right of the main MHV trunk without inflow control by Pringle maneuver. The major MHV tributaries and inferior right hepatic vein (IRHV) that exceeded 5 mm in diameter were confirmed by intraoperative ultrasonography and preserved.

Bench Surgery

When the donor graft had major MHV tributaries, the recipient's SFV was harvested for use as an interposition graft. The surgical technique for harvesting the SFV has been described previously.[10] In a basin, all major MHV tributaries were anastomosed to an SFV graft with use of continuous 6-0 prolene suture.

Recipient Operation

Total hepatectomy preserving the IVC was performed after reconstruction of MHV tributaries on the back table. Implantation was done following closure of the stump of the recipient's left hepatic vein. At first, the right hepatic vein (RHV) of the graft was anastomosed to the stump of the recipient's RHV in end-to-end fashion. The SFV interposition graft was anastomosed to the stump of the recipient's MHV using continuous suture. Direct anastomosis of the IRHV to the wall of the recipient's IVC was done in the presence of major IRHV. The graft was reperfused after reconstruction of the portal vein. The hepatic artery anastomosis was performed with microvascular instruments. Biliary reconstruction was accomplished by either choledochojejunostomy using a Roux-en-Y loop or duct-to-duct anastomosis.

RESULTS

The 11 consecutive adult-to-adult LDLT procedures were successful in all cases with a mean follow-up of 17 months (range 11–22 months). Of the 11 patients, 5 underwent liver biopsy due to moderate increases in serum transaminase levels and cholestasis during the first postoperative month. All 5 biopsies had no evidence of typical venous congestion or rejection.

The anatomical variations of all reconstructed hepatic veins in RLG are summarized in Table 1 Reconstruction of hepatic outflow on the back table significantly prolonged the cold ischemic time in group 1 patients (median, 161 minutes; range, 146–452 minutes) compared with that in group 2 patients (median, 74 minutes; range, 74–77 minutes). The warm ischemic time (WIT) for group 1 (median, 56 minutes; range, 40–68 minutes) was longer than that for group 2 (median, 48 minutes, range, 36–56 minutes). However there was no significant difference between the two groups with regard to WIT, which represented the duration of hepatic and portal venous reconstruction.

Although the median peak levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for group 1 were higher than those for group 2, no patient in either group showed a marked elevation of AST and ALT on postoperative days 14 and 30 (Table 2). Except for one patient (case 10), bilirubin levels were less than 3 mg/dL on postoperative day 14. Changes over time in bilirubin levels were similar for the two patient groups.

Table 2. Postoperative Liver Function Tests of 11 Patients With (Group 1) or Without MHV Reconstruction (Group 2)

	Peak		14 pod			30 pod		
	AST (IU/dL)	ALT (IU/dL)	AST (IU/dL)	ALT (IU/dL)	T-Bil (mg/dL)	AST (IU/dL)	ALT (IU/dL)	T-Bil (mg/dL)
Group1 (n = 8)	177 (66–792)	176 (88–585)	38 (16–70)	65 (17–151)	1.9 (0.9–5.6)	31 (10–49)	72 (12–118)	1.0 (0.6–1.5)
Group2 (n = 3)	97 (83–174)	146 (53–215)	33 (21–85)	51 (17–121)	1.6 (1.0–3.2)	23 (22–28)	66 (50–92)	1.3 (0.9–1.6)

Abbreviations: pod, postoperative day; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Continuous data are expressed as median and range.

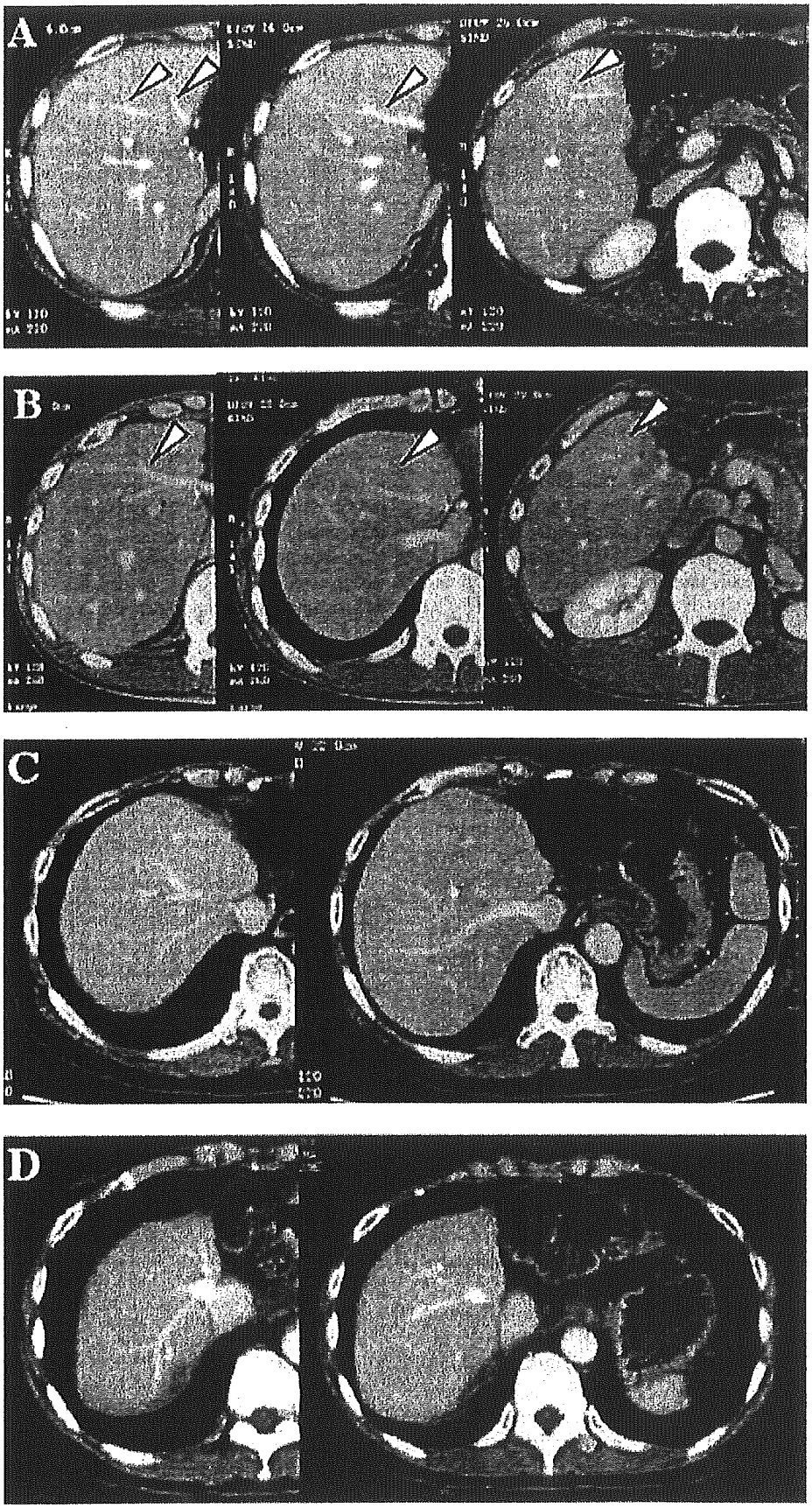

Fig 1. Computed tomographic images obtained 4 weeks after transplantation. **(A, B)** Right-lobe liver grafts with middle hepatic vein (MHV) reconstruction using recipient's superficial femoral vein. The MHV tributaries draining into segments 5 and 8 are shown with arrowheads. **(C, D)** Right-lobe liver grafts without MHV reconstruction due to lack of major MHV tributaries. There was no perfusion defect in the anterior segment in these patients.

The median preoperative ratio of graft volume to recipient standard liver volume (GV/SLV) for group 1 was 54.7% compared with 58.5% for group 2 patients. The median estimated GV/SLV ratio at 4 weeks' postprocedure was 96.5% for group 1 and 85.7% for group 2. A significant difference existed in estimated GV/SLV ratios at 4 weeks' postprocedure between the two groups, but not in the regeneration rate of the anterior and posterior segments. In all 8 patients in group 1, dynamic enhanced-computed tomography (CT) at 4 weeks' postoperation revealed a patent interposition SFV graft (Fig 1A, B). Among the 3 patients in group 2, one patient (case 8) showed relatively poor regeneration at 4 weeks' postprocedure per CT imaging (Fig 1D). This patient was a 35-year-old woman who received a RLG with lack of major MHV tributaries from her 64-year-old father. According to CT volumetry, her liver volume 4 weeks after LDLT was 708 mL, which represented 65.6% of the standard liver volume.

Of the 8 patients in group 1 (all of whom underwent SFV harvesting), 4 (50%) developed transient leg edema without skin changes that was easily managed with graded compression stockings.

DISCUSSION

Reconstruction of hepatic venous outflow is critical in left-lobe or right-lobe LDLT. Hepatic venous outflow impairment has been recognized in right-lobe liver grafts deprived of MHV tributaries. Some patients who did not undergo venous reconstruction developed severe graft dysfunction that resulted in death.[11] Although several indications for reconstruction of MHV tributaries have been proposed,[4,12] we have reconstructed all major MHV tributaries greater than 5 mm. In the current series, postoperative peak values of AST and ALT in cases of RLG with MHV reconstruction indicated that mild hepatic venous congestion was evoked, particularly in the first postoperative week, despite MHV reconstruction. In addition, enzyme values were less than 250 IU/dL in cases of RLG with lack of dominant MHV tributaries, suggesting that outflow from the anterior segment had already developed to drain into the RHV system.[13] It is impossible to reconstruct all negligible MHV tributaries, no matter how excellent the surgical techniques. Complete MHV replacement in a RLG, however, would not be feasible even if it was deemed necessary. Therefore, it should be noted that the extended right-lobe liver graft is an ideal graft for the recipient with regard to venous outflow of the anterior segment,[1] although the donor may face potential risks.

When there is a necessity for multiple reconstructions of venous outflow, cryopreserved vein graft composites, including common and external iliac veins, may be useful to minimize WIT.[8] If these techniques, which use cryopreserved vein grafts obtained from a deceased donor, are not available, reconstruction of the MHV must be performed using an autologous vein graft. The GSV is commonly utilized for such reconstructive procedures, although the GSV is sometimes inadequate for reconstruction of the MHV due to differences in caliber and wall thickness. To overcome these intraoperative dilemmas, Lee and associates[3] reconstructed MHV tributaries with two sheets of the GSV. Moreover, experience has shown that recipient left portal vein, even in cases with a patent umbilical portion of the vein, is often inadequate in length as an interposition graft when the major orifice of the MHV branch draining segment 5 is far apart from that of the RHV. Kornberg and associates[7] described MHV reconstruction using autologous SFV. They reconstructed two major MHV tributaries by using two interposition SFV grafts. We reconstructed all MHV tributaries with a single-vein interposition graft to reduce WIT. Although SFV harvesting has been demonstrated to be a safe procedure in vascular surgery,[9,10] major concerns remain regarding possible long-term venous morbidity associated with deep-vein removal after liver transplantation.

In summary, a recipient SFV graft is an excellent alternative conduit for MHV reconstruction in the absence of a venous system from a deceased donor.

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ORIGINAL ARTICLE

Risks of donation and quality of donors' life after living donor liver transplantation

Shigehito Miyagi, Naoki Kawagishi, Keisei Fujimori, Satoru Sekiguchi, Tatsuya Fukumori, Yorihiro Akamatsu and Susumu Satomi

Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine, Sendai, Japan

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Correspondence
Shigehito Miyagi MD, PhD, Division of Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. Tel.: +81-22-717-7214; fax: +81-22-717-7217; e-mail: msmsmiyagi@yahoo.co.jp

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Summary

The purpose is to clarify risks of donation and quality of the donor's life after living-related donor liver transplantation (LDLTx). Sixty-eight donors were classified into four groups: lateral segment group ($n = 30$); left lobe group ($n = 18$); left lobe with the middle hepatic vein group ($n = 11$); right lobe group ($n = 9$). We investigated (i) the risks of donation, and evaluated the following: blood loss, operation time, postoperative liver function and duration of hospitalization; (ii) quality of donors' life: donors were mailed a structured questionnaire and the Short-Form Health Survey (SF-36), a generic measure assessing quality of life using eight scales. The results were: (i) there were no differences in liver function and duration of hospitalization between four groups; (ii) 48 donors (71%) responded. All donors returned to normalcy. The donors did not regret their decision to donate except two cases whose recipients had died. The donors' life was almost guaranteed regardless of the lobe we used as the graft.

Introduction

Liver transplantation (LTx) has been established as the standard therapy for end-stage liver disease. But in recent years there is shortage of donors all over the world [1]. To compensate for the shortage of donor grafts, living-related donor liver transplantation (LDLTx) is globally accepted. LDLTx provides potential recipients with timely transplantation, but the procedure is associated with risks to the donor. In LDLTx the donor is exposed to the risks inherent to a surgical operation, and the donor might experience a considerable psychological burden [2]. Therefore, the safety of the donor operation and donors' life after the operation must be guaranteed while maintaining the viability of the graft. For the healthy volunteer donor, classic endpoints (i.e. control of disease, disease-free survival, return to normal activities, etc.) do not apply. For donors, any benefit of donation is primarily a psychological point of view [3,4]. Although the use of grafts from living kidney donors is common, and considerable data exists regarding the psychological impact of donation [5–7], there are only a few reports about psychosocial outcomes of living liver donors [8–10] except for the reports about donors who provided left lateral segments. There are no reports about the comparison of the psychosocial outcomes of donors who provided left lobe and those who provided right lobe in a single medical centre. Furthermore there are only a few reports, which mentioned about the relationship between the complications of donor or recipients' operation and psychosocial outcomes of donors. The purpose of this study was to clarify the risks of the donor operation and the quality of the donor's life after LDLTx for a long-term.

In our institute we have performed 68 LDLTx from July 1991 to July 2003. We transect the donor liver without using the vascular occlusion technique [11]. We retrospectively reviewed the safety of our donor operations based on parameters such as blood loss, blood transfusion, operation time, duration of hospitalization and complications. In addition, we surveyed our donors' data, which were classified into four groups by the parts of the liver grafts, to learn how they perceived their experience.

Patients and methods

Informed consent was obtained from both donors and recipients. All procedures were reviewed and approved by the ethical committee of Tohoku University School of Medicine and have therefore been performed in accordance with the ethical standards of the Declaration of Helsinki.

Sixty-eight donors for LDLTx received the liver resection in Tohoku University Hospital from July 1991 to July 2003. Age ranged from 17 to 64 years and male:female ratio was 33:35. Their mean age, weight and height were 34.7 ± 8.8 years old, 56.7 ± 7.8 kg and 162.6 ± 8.2 cm, respectively. None of the donors showed abnormal data in blood tests on preoperative assessment. We transected the donor liver without using the vascular occlusion technique [11].

Donors were classified into four groups: (i) lateral segment (LS) group ($n = 30$); (ii) left lobe (LL) group ($n = 18$); (iii) left lobe with the middle hepatic vein (LLM) group ($n = 11$); (iv) right lobe (RL) group ($n = 9$). We investigated (i) the risks at the donor operation and (ii) quality of donors' life at a mean of 1665.3 ± 1113.4 days after donation.

Postoperative complications

Blood loss, blood transfusion, operation time, postoperative liver function, complications and the length of hospitalization were evaluated.

Long-term quality of life of donors after LDLTx

Donors were mailed a structured questionnaire about the general health, present occupational status and 'what you think now about LDLTx' (Table 1). In addition, donors completed the Short Form, 36-question Health Survey (SF-36), a generic measure of quality of life [12,13]. The self-administered SF-36 survey assesses eight health domains: (i) physical functioning, (ii) physical role limits, (iii) emotional role limits, (iv) vitality, (v) pain, (vi) mental health, (vii) social function and (viii) general health.

We also reviewed recipient outcomes (i.e. major complications or death) and analysed the effect of recipient outcome on donors' SF-36 scores.

Statistics

Values are given as mean ± SD. Student's *t*-test and one-way ANOVA were used to compare categorical data. $P < 0.05$ were considered to be significant. All calculations were made with the StatView software package (SAS Institute, Cary, NC, USA).

Table 1. Structured questionnaire for donors after donation.

1. Are you tack at work
   1 yes
   2 no
2. General health*
   1 Good
   2 Not so good
   3 Bad
   4 In the hospital
3. What you think now about LDLTx
   1 Not regret
   2 Regret

*Are there any new medical symptoms which you relate to the surgery?

Results

Postoperative complications

The weight and height of the donors are given in Table 2. There were no significant differences in weight and height among the four groups, but the average age in the LL and LLM groups was significantly higher than that in the LS group ($P = 0.036$ LL versus LS; $P < 0.001$ LLM versus LS). The weight of the graft in the RL group was significantly more than that in the other three groups (LS, LL, LLM) ($P < 0.001$). The operation time in the LL and LLM groups was significantly longer than that in the LS group ($P = 0.007$ LL versus LS; $P = 0.011$ LLM versus LS) (Table 2).

Blood loss volume in the LLM group was significantly higher than that in the LS and LL groups ($P < 0.001$ LLM versus LS; $P = 0.009$ LLM versus LL). Maximum total bilirubin in the LLM and RL groups was significantly higher than that in the LS group ($P = 0.046$ LLM versus LS; $P = 0.014$ RL versus LS). But maximum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) showed no significant differences among the four groups. There were also no significant differences in the duration of hospitalization among the four groups. Heterologous blood transfusion was not required except for one donor of the LLM group (Table 2).

Postoperative complications occurred in three donors in the LS group, one in the LL group, four in the LLM group and two in the RL group (Table 3). Most postoperative complications were treated without surgical procedure. A donor in the LL group, suffering from sepsis and respiratory distress secondary to the intra-abdominal abscess, was subjected to a drainage operation and was discharged after 64 days of hospitalization. Most of the major complications, such as bile leakage and intra-abdominal abscess occurred at an early period after we started LDLTx. Apart from the donor who had undergone the drainage operation, only several minor complications

Table 2. Age, weight, height, graft weight, operation time, blood loss, postoperative liver function, and hospitalization.

	LS (n = 30)	LL (n = 13)	LLM (n = 11)	RL (n = 9)
Age (years)	30.2 ± 6.0	37.1 ± 5.3*	43.0 ± 10.5*	34.9 ± 11.9
Weight (kg)	54.9 ± 7.5	57.5 ± 6.5	61.8 ± 10.0	55.2 ± 6.3
Height (cm)	162.6 ± 7.5	162.3 ± 8.7	163.3 ± 9.4	162.2 ± 9.0
Graft weight (g)	220 ± 30.1	285 ± 46.6*	372 ± 63.7*†	553 ± 84.3*†‡
Operation time (min)	453 ± 70	544 ± 72*	541 ± 136*	443 ± 73
Blood loss (ml)	490 ± 273	722 ± 331	1201 ± 702*†	883 ± 346
Heterologous blood transfusion	0/30	0/18	1/11	0/9
Postoperative liver function				
AST Max	319 ± 247	298 ± 170	306 ± 178	294 ± 104
ALT Max	393 ± 242	334 ± 151	412 ± 281	291 ± 97
T-bil Max	1.5 ± 0.6	2.5 ± 1.4	2.7 ± 1.6*	2.9 ± 1.1*
Mean hospitalization time (days)	10.9 ± 4.7	11.8 ± 13.3	14.1 ± 11.4	11.2 ± 3.2
Mean follow- up time (days)	1608 ± 960	2347 ± 1095	1866 ± 930	249 ± 214

*P < 0.05 versus LS group; †P < 0.05 versus LL group; ‡P < 0.05 versus LLM group.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Complications of donors.

	LS (n = 30)	LL (n = 13)	LLM (n = 11)	RL (n = 9)
Age (years)	30.2 ± 6.0	37.1 ± 5.3*	43.0 ± 10.5*	34.9 ± 11.9
Complications	3/30	1/18	4/11	2/9
Biliary leakage	2 (cases 2, 44)	1 (case 6)	1 (case 4)	0
Wound infection	1 (case 2)	1 (case 6)	2 (cases 28, 37)	0
Intra-abdominal abscess	1 (case 2)	1 (case 6)	0	0
Sepsis., DIG	0	1 (case 6)	0	0
Prolongation of liver dysfunction	0	0	1 (case 4)	0
Ileus	0	0	1 (case 48)	0
Abdominal wall hernia	0	0	0	1 (case 62)
SMV thrum to sis	0	0	0	1 (case 54)

*P < 0.05 versus LS group.
DIC, disseminated intravascular coagulation.

were experienced by other donors. The overall incidence of complications was 13.2% (nine of 68) and that of biliary complication was 5.9% (four of 68). The overall incidence of wound infection was also 5.9% (four of 68). All donors returned to their normalcy within 1 year. There was no donor death in our series (Table 3).

Long-term quality of life of donors after LDLTx

Forty-eight donors (71%) responded at a mean of 1538.2 ± 1194.1 days after donation. But the response rate of donors whose recipients had died was 40.0%. All donors returned to normalcy, and no one was hospitalized (Table 4). Donors did not regret their decision to donate except for two cases whose recipients had died (LS = 1, LLM = 1).

Compared with published Japanese norms (n = 3395) [13] in SF-36, our donors scored similar or higher than the general population (Table 5). Donors whose recipients had major complications scored significantly lower on the mental and general health scale than those whose recipients had no major complications, but those donors still scored as well as the general population on the mental and general health scale. There were no significant differences between the donors who had complications and the donors who had no complications in all eight domains. There were also no significant differences among the four groups (LS, LL, LLM and RL) in all the eight domains.

Discussion

In this study, we retrospectively reviewed the safety of our donor operations based on various parameters. In addition, we surveyed our donors to find out as to how they perceived their experience. As a result, there were no significant differences among the four groups in maximum AST, maximum ALT and the duration of the hospitalization. There were no donor deaths in our series and the safety of donor operation was guaranteed no matter which lobe was used as the graft. Furthermore, in psychosocial outcomes of living liver donors, they did not regret

Table 4. Quality of donors' life based on our structured questionnaire.

	LS (n = 30)	LL (n = 13)	LLM (n = 11)	RL (n = 9)
The number of reply	19 (63.3%)	13 (72.2%)	7 (63.6%)	9 (100%)
Mean follow-up time	1608 ± 960	2347 ± 1095	1866 ± 930	249 ± 214
Present occupational status	19 (100%)	13 (100%)	7 (100%)	9 (100%)
General health				
Good	15 (78.9%)	12 (84.6%)	7 (100%)	9 (100%)
Not so good	3 (15.8%)	2 (1 5.4%,)	0	0
Bad	1 (5.3%)	0	0	0
In the hospital	0	0	0	0
What you think now about LDLTx				
Not regret	18	13	6	9
Regret	1	0	1	0

Table 5. Quality of donors' life based on SF-36 survey.

	Mental health	Role (emotional)	Social function	Vitality function	Physical	Role (physical)	Bodily pain	General health
US norm	74.7 ± 18.1	81.3 ± 33	83.3 ± 22.7	60.9 ± 21	84.2 ± 23.3	81 ± 34	75.2 ± 23.7	72 ± 20.3
Japanese norm	72.7 ± 19.2	83.8 ± 31.5	86.2 ± 19.4	65.3 ± 20.4	87.9 ± 15.5	85.3 ± 29.0	76.2 ± 22.7	65.0 ± 19.6
Japanese norm (30–39 years old)	72.6 ± 17.6	86.4 ± 28.8	87.1 ± 17.3	65.9 ± 19.0	92.6 ± 9.6	90.5 ± 22.6	77.2 ± 21.0	67.8 ± 17.0
All donors	86.4 ± 15.4	84.7 ± 26.6	93.7 ± 13.1	82.5 ± 16.4	95.8 ± 5.7	86.5 ± 18.6	86.2 ± 16.6	81.6 ± 17.6
No recipient complications	88.5 ± 14.1*	85.4 ± 27.9	93.9 ± 13.7	83.0 ± 15.7	96.5 ± 5.6	88.4 ± 18.6	86.9 ± 16.9	86.8 ± 11.6*
Recipients with complications	74.3 ± 18.0	81.0 ± 17.8	92.9 ± 9.8	79.3 ± 20.9	92.1 ± 4.9	75.0 ± 14.4	82.1 ± 15.8	68.6 ± 26.9
No donor complications	87.1 ± 14.4	85.4 ± 26.9	93.6 ± 13.7	82.9 ± 15.7	96.5 ± 5.6	87.2 ± 18.6	87.3 ± 16.9	82.4 ± 16.2
Donors with complications	82.3 ± 21.3	81.0 ± 26.2	94.6 ± 9.8	80.0 ± 21.0	92.1 ± 4.9	82.1 ± 18.9	79.7 ± 14.1	77.3 ± 25.2

*$P < 0.05$ versus recipients with complications.

their decision to donate except for two cases whose recipients died (LS = 1, LLM = 1) and all donors returned to normalcy within 1 year.

In our institute, the first LDLTx performed was that of an adult to a child in 1991. In 1997, we performed our first adult-to-adult LDLTx. We retrospectively assessed 68 donor operations and found that severe complications had occurred only in the early period after we started LDLTx at our hospital. However, in most cases the donors recovered without the need for surgical treatment. Recent donors developed no major complications. The decrease of donor complications was associated with the improvement of our surgical procedure. Only after one of the donors had undergone drainage operation because of biliary injury, intraoperative cholangiography was performed in all cases, which effectively prevented biliary injuries, decreasing the incidence of major complications. Renz and Roberts [14] reviewed the long-term complications of LDLTx. They reported routine donor hospital stays of less than 10 days; average donor blood losses were approximately 400–800 ml, and the need for heterologous blood transfusion for the donor was uncommon. Moreover, they reported an overall incidence of complications ranging from 15% to 20%. Biliary complications were the most commonly reported source of donor morbidity with an overall incidence of 5–10%. In the report of Japanese Liver Transplantation Society [15], donor hospital stays were 15.6 days and heterologous blood was given to 21 (1.1%) donors. The incidence of postoperative complications was 12.4% and that of biliary complication, which was also the most commonly complication, was 4.0%. But in the right graft group, the incidence of biliary complications was 10.2%. Compared with these data, donor hospital stays (11 days), average donor blood losses (718.5 ml) and the need for heterologous blood transfusion for the donor were similar in our institution. The overall incidence of complications was 13.2% and that of biliary complication was 5.9%. On the contrary, in the RL group, the incidence of biliary complications was 0%. In our institute there were no significant differences among the four groups in maximum AST, maximum ALT and the duration of hospitalization (Table 3). The safety of donor operation was guaranteed regardless of the lobe we used as the graft.

There has been limited information about psychosocial risks to living liver donors. But in a recent study by Johnson *et al.* [5] on long-term follow-up of 524 living kidney donors using the SF-36 survey, donors reported a better quality of life than the national norm. Generally, published reports on kidney donors indicate that

donors had an improved sense of well-being and self-esteem after donation [5–7]. In our study about psychosocial outcomes of living liver donors, they did not regret their decision to donate except for two cases whose recipients died. All donors returned to normalcy, with no negative impact on social or business interactions.

The results of the SF-36 demonstrated that compared with the published US and Japanese norms in all eight domains measured, the living donors scored well. With regard to general health and mental health, the results highlight the impact of the recipient's course on donor psychosocial outcome after donation (Table 5). The donors whose recipients had major complications scored significantly lower on the mental and general scale than those whose recipients had no major complications. There were no significant differences between the donors who had complications and the donors who had no complications in all the eight domains. In the living kidney donor study by Johnson *et al.* [5] and living liver donor study by Kim-Schluger *et al.*[10] similar results were found. The donors whose recipient died were more likely to say that they would not donate again.

We recognize that our brief survey could not expose some of the deeper and more complex personal issues that affect the quality of life and potential feelings of regret or resentment after donation. In addition, donors were undoubtedly aware that their responses were not anonymous and might in fact be seen by the member of the team responsible for the care of their recipients. We thought that the survey results should be reviewed by independent researchers blinded to the identity of the respondents. But if we adopted this method, it was nearly impossible to classify the groups of donors and to investigate donors' and recipients' complications. So it needs further consideration.

Furthermore we recognized that our study was limited. In fact only 71% of donors responded and 29% of donors did not respond. Moreover the response rate of donors whose recipients had died was only 40.0%. Possible reasons for the lack of response included the fact that some of them moved out and some of them, whose recipients had died, did not want to remember the transplantation. We could not disregard the possibility that these donors might be less satisfied with their experiences.

Living donor LTx has changed the way of the management for the end-stage liver disease. It is a promising option to resolve end-stage liver disease. Safe donor operation allows more patients to receive life-saving liver transplants. However the safety of donors is not 100% guaranteed. So, we must ensure that quality of life after donation remains a primary outcome measure when we consider the utility of LDLTx.

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Usage of Deoxyspergualin on Steroid-Resistant Acute Rejection in Living Donor Liver Transplantation

NAOKI KAWAGISHI, KAZUSHIGE SATOH, YOSHITAKA ENOMOTO, YORIHIRO AKAMATSU, SATOSHI SEKIGUCHI and SUSUMU SATOMI

Division of Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University, Sendai, Japan

KAWAGISHI, N., SATOH, K., ENOMOTO, Y., AKAMATSU, Y., SEKIGUCHI, S. and SATOMI, S. *Usage of Deoxyspergualin on Steroid-Resistant Acute Rejection in Living Donor Liver Transplantation.* Tohoku J. Exp. Med., 2006, **208** (3), 225-233 —— Deoxyspergualin (DSG) is an immunosuppressive agent used to treat steroid-resistant acute rejection after kidney transplantation. But in the case of acute rejection after liver transplantation, DSG was reported effective in just a few cases. From July 1991 to November 2005, 96 patients underwent living donor liver transplantation (LDLTx) in our institution. Of them, 9 patients, including 4 ABO incompatible recipients, are presented. Rejection symptoms that did not respond to steroid pulse therapy (methylprednisolone, 10-20 mg/kg/day for 3 days) and were treated with DSG (3 or 5 mg/kg/day) for 4 to 14 days together with a maintenance dose of the steroid. Among them, five responded to treatment with DSG, two did not respond and the other two patients were not evaluated. Six of the nine patients are symptom free at present. Complications such as leukopenia and thrombocytopenia were successfully treated with granulocyte-colony stimulating factor or by platelet transfusion. No recipient died as a direct consequence of the complications induced by DSG. DSG proved effective and safe for some of the LDLTx recipients with steroid-resistant acute rejection but it was not effective for the treatment of accelerated humoral rejection in ABO incompatible recipients. ———— liver transplantation; living donor; deoxyspergualin (DSG); rejection; ABO incompatibility

Deoxyspergualin (DSG) was isolated in the 1980's from the *Bacillus laterosporus* found in Japanese fields (Takeuchi et al. 1981). It was initially expected to be an antitumor antibiotic, but it also had special immunosuppressive effects. As for the mechanisms of the immunosuppressive reaction, it was reported that this was not induced by its inhibitory effect on the production of monokines by macrophages or of interleukin-2 by T lymphocytes, but by its cytostatic effect, that is, the inhibition of the cell cycle at the G0/G1 phase (Nemoto et al. 1987). It also inhibited the maturation of T lymphocytes and the activation, differentiation and maturation of B cells, thereby inhibiting antibody production (Fujii et al. 1990). The immunosuppressive effect of DSG increased with the duration of treatment and DSG was not absorbed from the intestine (Nemoto et al. 1987). Therefore, DSG was recognized as an immunosuppressive agent that could be administered at

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Correspondence: Naoki Kawagishi, Division Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.
e-mail: kawan@mail.tains.tohoku.ac.jp

high doses for a short period. The results of phase I and phase II clinical trials showed that DSG was useful in several situations: (i) prophylaxis and treatment of acute rejection, (ii) prevention of antibody response to biologic agents used for immunosuppression, (iii) suppression of the humoral response at the time of transplantation in sensitized patients, and (iv) inhibition of macrophage-mediated damage of cellular transplantation (e.g., islets) (Wahoff et al. 1996). In a randomized study of DSG vs anti-CD3 monoclonal antibody (OKT3) for the treatment of steroid-resistant acute rejection in renal transplantation, no significant difference in efficacy was found between the two groups (Ohkubo et al. 1993). However, the side effects profile of DSG was significantly better than that of OKT3 (Ohkubo et al. 1993).

In Japan, DSG has been licensed as an immunosuppressive agent for steroid-resistant acute rejection in patients subjected to kidney transplantation since 1994. Thereafter, it was revealed that DSG had novel immunosuppressive effects including the reversion of an established rejection and suppression of the antibody response seen in subsets of sensitized patients (Okazaki et al. 1989). But the efficacy of DSG in patients undergoing liver transplantation is still unknown. Some reports indicated that DSG was effective against acute rejection in sensitized patients as well as in kidney recipients (Kato et al. 1997). In our institution, we have treated 9 LDLTx recipients with DSG for acute cellular and humoral rejection, including 4 patients with ABO incompatibility. In this study, we describe the effects of DSG on steroid-resistant acute rejection in living donor liver transplant recipients.

Patients and Methods

Characteristics of the patients

From July 1991 to November 2005, 96 LRLTx were performed in pediatric and adult patients with end-stage liver disease in the Division of Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University. This program was approved by the ethics committees of Tohoku University Hospital and the patients gave their informed consent regarding LDLTx and the use of DSG for steroid-resistant acute rejection. Donors were selected among parents, brothers or sisters and spouses on the basis of liver function tests, serological markers of hepatitis, ABO blood group, graft/recipient size matching, lymphocyte cross-matching and human leukocyte antigen (HLA) typing. Among them steroid-resistant acute rejection occurred in 9 recipients. The primary diseases of the recipients were biliary atresia in 7, primary sclerosing cholangitis (PSC) in 1, and homozygous familial hypercholesterolemia (FH) in 1. Four recipients were ABO incompatible and 3 out of these 4 recipients were subjected to plasmapheresis (PP) and/or double filtrating plasmapheresis (DFPP) because of the high antibody titers they had before transplantation. After transplantation, apheresis was performed to eliminate antibodies in 3 recipients, PP in 2 and PP with continuous hemodiafiltration (CHDF) in 1 (Table 1). In ABO incompatible recipients, an IgM titer of more than 16 was the indication for apheresis. One ABO incompatible recipient was not subjected to apheresis because the antibody titer against donor blood type was low. These 9 recipients consisted of 4 males and 5 females.

Primary immunosuppressive therapy

The immunosuppressive regimen consisted of cyclosporine (CsA), tacrolimus (TAC), azathiopurine (AZ) and methylprednisolone (MP). Seven of the 9 recipients were administered TAC initially while the other 2 were administered CsA. TAC was administered orally 12 hrs before transplantation at a dose of 0.075 mg/kg, and from day 1 after transplantation at a dose of 0.1-0.2 mg/kg/day via a nasogastric tube. On the day of transplantation CsA was administered orally or via a nasogastric tube at a dose of 8 mg/kg/day. The doses of TAC and CsA were adjusted according to plasma trough levels. MP was administered intravenously at a dose of 20 mg/kg/day at the time of the operation and then tapered to 1 mg/kg/day during one week. In the ABO incompatible recipients AZ was administered orally or intravenously from Day 3 before transplantation at a dose of 2 mg/kg/day. In one recipient TAC was switched to CsA because of difficulty in maintaining a suitable trough level.

Rescue therapy for rejection

When symptoms of rejection did not improve with steroid pulse therapy (10-20 mg/kg/day for 3 days), DSG (3 or 5 mg/kg/day) was administered daily for 4 to 14 days together with a maintenance dose of TAC and the

steroid. When the recipient had leukopenia (WBC < 3,000/mm^3) or thrombocytopenia (Plt. < 50,000/mm^3), granulocyte colony stimulating factor (G-CSF) (1-2 μg/kg) was administered or platelets were transfused. PP or CHDF was performed if humoral rejection occurred in the ABO incompatible recipients.

Diagnosis of rejection

Protocol liver biopsies were taken at the time of transplantation and after surgery percutaneous fine needle biopsy was performed under ultrasonography when rejection was clinically recognized. Biopsy specimens were formalin-fixed and parafin-embedded. Five-μm-thick sections were stained with hematoxylin-eosin and Masson's trichrome for collagen. Individual histological features were scored according to a semiquantitative scoring system, which included the following parameters: degree of portal inflammation, piecemeal necrosis, lobular necrosis, steatosis, fibrosis, portal and central vein endothelitis, acute cholangitis, ductular regeneration and cholestasis. Acute ischemic damage was defined by the presence of confluent central or lobular necrosis associated with a variable degree of swelling and bile staining (cholestasis) and without evidence of inflammatory reaction (International Workshop Party 1995). Acute graft rejection was diagnosed by the concomitance of mixed portal inflammation coupled with bile duct inflammation and/or subendothelial inflammation of portal and terminal hepatic veins, according to international criteria (International Workshop Party 1995). Rejection was classified as mild, moderate, or severe.

Monitoring of anti-ABO alloantibodies

The presence of ABO allo-antibodies was assessed in all ABO incompatible patients 2 weeks before transplantation. Serum samples were analyzed with respect to agglutinin titer against a 2 percent suspension in saline of type A or B red blood cells (RBC) after incubation for 1 hour at room temperature. The titer of IgG antibodies was determined by treating the serum samples with 0.01M dithioethreitol (DTT), followed by incubation for 1 hour at 37°C with type A or B RBC. After repeated washings, polyspecific anti-human globulin serum was added. Changes in ABO antibody titers were expressed as the reciprocal number of the highest serum dilution that caused macroscopic agglutination. After transplantation, anti-A or -B alloantibodies were measured every day for the first 7 days and then twice a week.

Apheresis

PP was performed using a continuous blood flow separator (OP-02^{TM} or OP-05^{TM}, Asahi Medical Co., Tokyo). As a second filter for DFPP, Evaflux^{TM} (Kuraray Co., Tokyo) was used. CHDF was performed using a high-performance membrane (PANFLO^{TM}, Asahi Medical Co.). For a blood access, a double-lumen catheter was placed in the subclavian or femoral vein. Replacement fluids were fresh frozen plasma of AB blood type group or 5% albumin in PP. Nafamostat mesilate (0.15 mg/kg/h) was given as the anticoagulant. PP or DFPP was performed before transplantation on 3 consecutive days in the patients with ABO incompatibility.

Results

Effectiveness for steroid resistant acute rejection

Acute rejection was initially treated with steroid pulse therapy; steroid-resistant acute rejection was occurred once in 9 recipients. They were administered DSG at the dose of 3 or 5 mg/kg/day daily for 4 to 14 days together with the maintenance dose of the steroid (Table 1).

Case 1: The patient was a 5-year-old girl with biliary atresia (BA). She received an ABO incompatible partial liver graft from her mother. Preoperatively PP and DFPP were performed because her anti-A antibody titer was high. On post operative day (POD) 6 liver function tests and histological biopsy indicated acute cellular rejection. She was treated with MP for 3 days. On POD 14 the values of her liver function parameters increased again and the biopsy showed acute cellular rejection. The patient was administered MP followed by DSG at the dose of 3 mg/kg/day for 10 days together with TAC and AZ. PP was also performed to treat her hyperbilirubinemia. After the administration of DSG the value of her liver function parameters decreased and she was discharged on POD 86. During her post operative course no accelerated acute rejection was observed and the anti-A antibody titers decreased after POD 7.

Case 2: The patient was a 1-year-old girl with BA. On POD 6 portal vein thrombosis was detected and thrombectomy was performed under

TABLE 1. *Patient demographic characteristics*

No. of Case	Age at Tx/ Gender	P.D.	Blood Type	P.I.	Treatment for Steroid Resistant Acute Rejection	Day on DSG Administration	Outcome
1	5y2m/F	BA	incompatible (A→O)	TAC, AZ, MP	DSG (3 mg/kg/day, 10 days) + PP	19 POD	effective
2	1y5m/F	BA	identical (A→A)	CsA, AZ, MP	DSG (3 mg/kg/day, 4 days)	13 POD	effective
3	11m/M	BA	incompatible (AB→B)	TAC, MP	DSG (3 mg/kg/day, 14 days) + MP	31 POD	effective
4	3y9m/F	BA	identical (A→A)	TAC, MP	DSG (3 mg/kg/day, 7 days 5 mg/kg/day, 3 days)	464 POD	ineffective
5	7y9m/M	BA	identical (O→O)	TAC, MP	DSG (3 mg/kg/day, 4 days)	1452 POD	effective
6	11m/M	BA	identical (B→B)	CsA, AZ, MP	DSG (3 mg/kg/day, 5 days)	14 POD	effective
7	5y11m/M	PSC	identical (B→B)	TAC, MP	DSG (3 mg/kg/day, 9 days)	26 POD	not evaluated
8	10y3m/F	BA	incompatible (A→B)	TAC, AZ, MP	DSG (3 mg/kg/day, 8 days) + splenectomy, PV cannulation, PP, CHDF	4 POD	ineffective
9	2y/F	HFH	incompatible (A→O)	TAC, MMF, MP	DSG (3 mg/kg/day, 10 days) + PP	5 POD	not evaluated

P.D., primary disease; P.I., primary immunosuppression; BA, biliary atresia; PSC, primary sclerosing cholangitis; DSG, deoxyspergualin; TAC, tacrolimus; CsA, cyclosporine A; AZ, azathioprine; MP, methylpredonisolone; PP, plasma pheresis; CHDF, continuous hemodiafiltration; PV, portal vein; HFH, homozygous familial hypercholesterolemia; MMF, mycophenolate mofetil; POD, post operative day.

laparotomy. The biopsy performed at the same time revealed signs of acute rejection. She was administered MP followed by DSG at the dose of 3 mg/kg/day for 4 days but it was discontinued because of severe leukopenia and thrombocytopenia. Her liver function started to improve on the day after discontinuation of DSG.

Case 3: The patient was an 11-month-old boy with BA (Fig. 1). He received an ABO incompatible partial liver graft from her mother. Apheresis was not performed before surgery because his anti-A antibody was low. On POD 18 the results of liver function tests and biopsy indicated acute cellular rejection. He was treated with MP for 3 days. However, the values of liver function parameters increased again and DSG was administered at the dose of 3 mg/kg/day for 14 days together with a 3-day course of MP pulse therapy. After the administration of DSG the concentration of total bilirubin decreased and he was discharged on POD 78. During his POD course no accelerated acute rejection was observed and the anti-A antibody titer remained low.

Case 4: The patient was a 5-year-old girl with BA. She had been discharged without any complication after LDLTx at the age of 3. One year after transplantation she developed post-transplant lymphoproliferative disease and her medication was changed from TAC to CsA. Then she developed acute rejection with severe bile duct damage; she was placed under MP pulse therapy followed by DSG at the dose of 3 mg/kg/day for 7 days and 5 mg/kg/day for 3 days. Her liver function improved but not dramatically; thus, she was administered acyclovir because viral hepatitis was also suspected. After these therapies her laboratory and clinical data gradually improved.

Case 5: The patient was an 11-year-old boy with BA. He had undergone LDLTx at the age of 7. He was administered DSG after the second pulse therapy but the values of his liver function

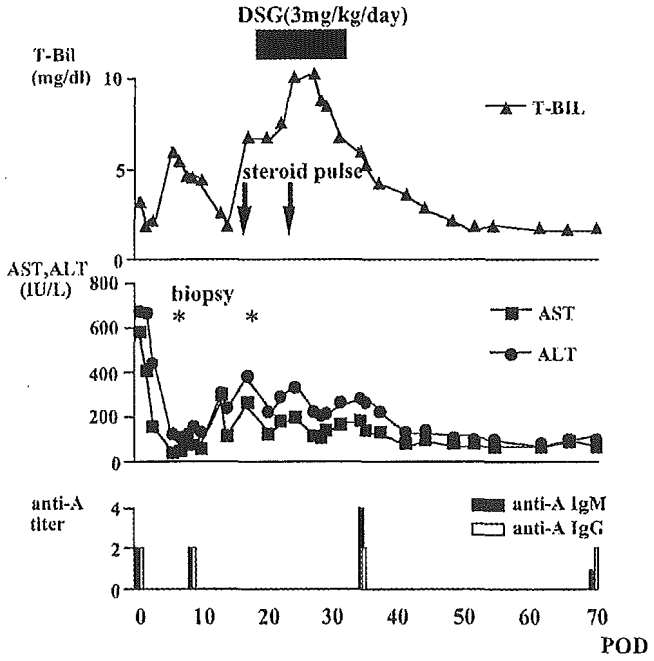

Fig. 1. Rescue therapy by DSG for acute cellular rejection.
Posttransplantation course of case 3. First steroid pulse therapy was ineffective, whereas DSG with MP pulse therapy resulted in improvement of liver function.
DSG, deoxyspergualin; T-Bil, total bilirubin.

parameters were still high after the 4th day on DSG. We speculated this was a case of drug-induced toxicity and withdrew the drug. The biopsy revealed the rejection reaction and drug-induced toxicity had ended. Thereafter his liver function gradually improved.

Case 6: The patient was a 10-month-old boy with BA. On POD 7 the values of liver function parameters and biopsy indicated acute cellular rejection. He was treated with MP for 3 days. However, the values of his liver function parameters increased again and he was administered DSG at the dose of 3 mg/kg/day for 5 days. His liver function improved but his white blood cells count decreased 2 days after the end of the DSG administration and he developed high fever. However, there was no infection and leukopenia improved after treatment with G-CSF.

Case 7: The patient was a 5-year-old boy with PSC. On POD 26 after pulse therapy, he was administered DSG but the value of his liver function parameters were still high after the 5th day on DSG. Examination of a biopsy specimen revealed no signs of rejection but of drug-induced toxicity. DSG was withdrawn on the 9th day of the administration. Thereafter, his liver function gradually improved.

Case 8: The patient was a 10-year-old girl with BA (Fig. 2). She received an ABO incompatible partial liver graft from her mother. Preoperative PP was performed because her anti-A antibody titer was high. On POD 4 the values of liver function parameters and biopsy indicated accelerated acute rejection. She was subjected to PP, splenectomy, MP pulse therapy and DSG. DSG was administered at the dose of 3

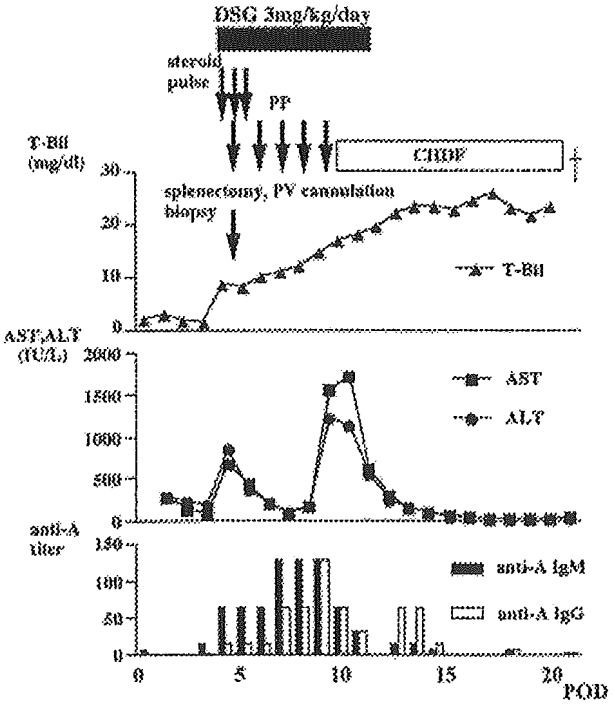

Fig. 2. Accelerated acute rejecion in case with ABO-incompatible.
Posttransplantation course of case 8. On 4 POD her liver function tests and histological biopsy indicated accelerated acute rejection. She was treated by PP, splenectomy, MP pulse therapy and DSG, however she was not rescued.
PP, plasmapheresis; CHDF, continuous hemodiafiltration; DSG, deoxyspergualin; T-Bil, total bilirubin.

mg/kg/day for 8 days together with PP. The titer of anti-A antibody decreased after the 9th POD but hyperbilirubinemia persisted. Her liver function gradually improved but she died on POD 22 because of cardiac failure.

Case 9: The patient was a 2-year-old girl with homozygous familial hypercholesterolemia. She received an ABO incompatible partial liver graft from her mother. Preoperative PP was performed because her anti-A antibody titer was high. On POD 3 the values of liver function parameters and anti-A antibody titer indicated humoral rejection. She was subjected to PP and DSG. DSG was administered at the dose of 3 mg/kg/day for 10 days together with PP. The titer of anti-A antibody decreased after POD 11. She suffered from biliary stenosis 6 months after LDLTx, but her liver function improved after percutaneous transhepatic biliary drainage.

Adverse events

As for adverse events, three recipients had leukopenia and/or thrombocytopenia and these were rescued by G-CSF or platelet transfusion (Table 2). Three recipients showed DSG-induced hepatotoxicity but their liver function tests improved within one week after withdrawal of the drug. None of the recipients died because of complications directly induced by DSG.

TABLE 2. *Adverse events observed during the anti-rejection therapy*

	n
Leukopenia	4
	(Use of G-CSF 2)
Thrombocytopenia	2
	(Platelet transfusion 1)
Drug induced toxicity	3

G-CSF, granulocyte colony stimulating factor.

Long-term follow-up

As for long-term follow-up, seven recipients are alive and six of them are symptom free at present (Table 3).

TABLE 3. *Long-term follow up*

No. of Case	Long term status	Period after LDLTx
1	symptom free	11y 5m (alive)
2	symptom free	11y 4m (alive)
3	symptom free	10y 5m (alive)
4	symptom free	9y 1m (alive)
5	symptom free	8y 10m (alive)
6	symptom free	8y 8m (alive)
7	recurrence of primary disease	7y5m (dead)
8	dead on 22 POD	-
9	biliary stenosis	1y (alive)

DISCUSSION

Steroid-resistant acute rejection is treated with DSG after living donor liver transplantation in our institution. Progressive graft rejection in a patient with a liver graft is life threatening and when steroids and/or other immunosuppressive agents fail to reverse the process retransplantation has been the only option. The cases described here show that DSG is effective for steroid-resistant acute rejection in living donor liver transplant recipients. DSG has been recognized as an effective immunosuppressive agent in kidney transplantation, particularly in Japan. The drug is mainly used as a prophylactic and/or rescue therapy for acute rejection. Particularly, in the case of rescue therapy for acute rejection after kidney transplantation, it was reported that therapy using DSG combined with MP was one-hundred percent effective while DSG alone was effective in more than 70% of the cases (Kenmochi et al. 1990). Moreover, it was reported that the efficacy of DSG and that of OKT3 against steroid resistant acute rejection were comparable (Ohkubo 1993).

In the field of liver transplantation there have been only a few reports that refer to the efficacy of DSG. Kato et al. (1997) reported 3 cases, including 2 ABO incompatible recipients, who were rescued by DSG after steroid-resistant acute cellular rejection. Groth et al. (1990) reported the reversal of acute rejection with DSG in a patient in whom previous treatment with steroid and

OKT-3 had failed. In our experience, DSG was effective for steroid-resistant acute cellular rejection in 6 out of 8 liver transplantation cases. But in one case with accelerated humoral rejection, DSG was not effective.

The precise mechanism of the immunological effect of DSG is not known but it is believed to inhibit a protein called heat shock protein 70, which is necessary for the translocation of transcription factors such as nuclear factor-kappa B (NF-kB) to the nucleus (Nadler et al. 1992). As a result, DSG inhibits not only the maturation of T lymphocytes but also the activation, differentiation and maturation of B lymphocytes, inhibiting thereby antibody production. Therefore, DSG is useful for sensitized or ABO incompatible recipients, relying on its ability to suppress humoral immunity. In the field of kidney transplantation, Okazaki et al. (1991) reported the efficacy of DSG in recipients after donor specific transfusion. In a study involving 44 ABO incompatible kidney recipients, in which DSG was used together with standard induction therapy, PP, splenectomy and local graft irradiation, the results of transplantation were excellent, i.e., graft survival was 83% at one year and 80% at three years (Takahashi et al. 1993). In liver transplantation, the efficacy of preformed lymphocytotoxic antidonor antibodies on graft survival still remains controversial. Several hypotheses have been proposed as possible explanations for the discrepancies among various studies (Donaldson et al. 1995; Manez et al. 1995). These discrepancies relate, in particular, to the relatively small numbers of patients as well as to methodological differences and sensitivity of the assays in renal transplantation.

As for liver transplantation, the survival rate of ABO incompatible patients has been reported to be significantly worse than that of ABO compatible patients (Farges et al. 1995). The presence of preformed anti A and/or anti B antibodies in the recipient and the wide expression of these antigens on endothelial cells in vessels and parenchymal epithelial cells in the graft are indeed risk factors for a hyper acute rejection (Ernst et al. 1984). Therefore, liver transplantation from ABO mismatched donors has been justified only in emergency cases, especially in children, due to the shortage of appropriate donor grafts. However, in living donor liver transplantation we have to use ABO mismatched grafts even in elective cases. In the case of blood type mismatched grafts, we take a lot of measures in an effort to succeed such as pre- and post- transplant PP, splenectomy and strong immunosuppressive therapy (Kawagishi et al. 2001). In our institution we experienced 11 patients who received an ABO blood type incompatible graft. We used DSG in four cases of acute cellular rejection and in two the therapy proved successful. But one patient with accelerated humoral rejection could not overcome severe rejection despite DSG combined with PP, splenectomy and portal cannulation (Case 8). In recipients of kidney transplants, it was reported that DSG was effective even for accelerated acute rejection (Amemiya et al. 1990).

The adverse effects observed in kidney transplant patients included numbness of the face, lips and limbs, gastrointestinal toxicity, bone marrow suppression and the occurrence of infection (Amemiya et al. 1990). In our experience none of the side effects, such as leukopenia, thrombocytopenia and drug toxicity, persisted for a long period. Infectious complications were prevented with antibiotics and stringent screening for bacterial and viral infection.

In conclusion, DSG proved effective for steroid-resistant acute rejection in some LDLTx recipients without inducing severe adverse effects. But DSG was not effective in patients with accelerated humoral rejection.

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Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience

Mureo Kasahara[a,*], Yasutsugu Takada[b], Hiroto Egawa[a], Yasuhiro Fujimoto[b], Yasuhiro Ogura[b], Kohei Ogawa[b], Koichi Kozaki[b], Hironori Haga[a], Mikiko Ueda,[b] and Koichi Tanaka[a,b]

[a] *Organ Transplant Unit, Kyoto University Hospital*
[b] *Department of Transplantation and Immunology, Kyoto University Faculty of Medicine, Kyoto, Japan*
* *Corresponding author: Mureo Kasahara, mureo@kuhp.kyoto-u.ac.jp*

Auxiliary partial orthotopic liver transplantation (APOLT) was initially indicated as a potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease to compensate for enzyme deficiency without complete removal of the native liver. We expand our indication of APOLT for small-for-size grafts to support the function of implanted grafts during the early post-operative period, and for ABO-incompatibility to sustain a patient's life if the patient has a graft failure.

We retrospectively reviewed 31 patients undergoing APOLT from living donor. The indication of APOLT was fulminant hepatic failure in 6, non-cirrhotic metabolic liver disease in 6, small-for-size grafts in 13 and ABO-incompatible cases in 6.

The cumulative survival rate for APOLT at 1 and 5 years was 57.9% and 50.6%, and 78.8% and 73.8% for standard LDLT. None of the patients who underwent transplantation with APOLT for fulminant hepatic failure had long-term patient survival. The incidence of acute cellular rejection was higher in APOLT (58.1%) than standard LDLT (35.0%). Biliary complication was higher and the need for retransplantation was greater in APOLT than standard LDLT ($p < 0.01$).

The results suggest that the indications of APOLT should be reconsidered in view of the risk for complications and retransplantation.

Key words: Auxiliary liver transplantation, living donor liver transplantation

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Introduction

Liver transplantation from a living donor is increasingly accepted with excellent results, usually in coordination with a cadaveric organ transplant program (1). In countries where cadaveric donors are limited, however, living donor liver transplantation (LDLT) is often the only treatment of choice for patients with end-stage liver disease (ESLD). The LDLT program in Kyoto University began in June 1990, and under this program 970 transplants in 920 patients have been carried out in the period up to November 2003. Because of the growing waiting list and the establishment of acceptable results of pediatric LDLT, we have been compelled to expand our indication of LDLT from small children to older children, and even to adults.

Analysis of our studies revealed poor graft survival in older patients receiving small-for-size grafts (2). To treat patients with a graft-to-recipient weight ratio (GRWR) of less than 0.8%, auxiliary partial orthotopic liver transplantation (APOLT) was indicated from 1996 (3). The rationale of APOLT for a small-for-size graft is that the remnant native liver is expected to support the function of the implanted graft during the early post-operative period. The graft liver expands its function in proportion to volume growth. After the graft liver has grown sufficiently, it can be expected to meet the hepatic functional demands of the recipient.

APOLT was initially indicated for potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease (4,5). The double aim of APOLT for fulminant hepatic failure is full native liver regeneration and discontinuation of immunosuppressive therapy (6). The auxiliary graft should support the remnant native liver during regeneration.

The advantage claimed for APOLT in non-cirrhotic metabolic liver disease is that it can compensate for enzyme deficiencies without complete removal of the native liver, which may have to aid the recipient in case of potential graft failure. The remaining native liver could benefit in the future from potential success in gene treatment (7,8).

The other potential indication for APOLT is ABO-incompatible transplantation. Transplants of ABO-incompatible grafts are often unavoidable due to the

limited number of potential donor candidates in the LDLT program. In our LDLT program, 12% of patients had to have an ABO-incompatible graft. A high incidence of early graft failure with a high rate of biliary and vascular complications in ABO-incompatible liver transplantation was reported (9). The remnant native liver could sustain a patient's life if the anticipated graft failure occurred in an ABO-incompatible case.

APOLT from living donors was performed in 31 cases for the following indications: (i) fulminant hepatic failure; (ii) non-cirrhotic metabolic liver disease; (iii) small-for-size graft and (iv) ABO-incompatibility. However, the safety of using this technique in ESLD patients remains open to question. The objective of the present study was to investigate the long-term clinical outcome of the APOLT studies in the Kyoto University LDLT program.

Patients and Methods

Study population

Since APOLT was first indicated in March 1995 for a patient with ornithine transcarbamylase deficiency (OTCD), 31 cases of APOLT have been performed at Kyoto University Hospital. There were 13 male and 18 female patients with a median age of 23 years (range: 1.4–53.7 years) and a median weight of 53.4 kg (range: 11.3–108 kg). The indication for transplantation was fulminant hepatic failure in 6 patients (hepatitis B virus [HBV]-related in 1 and of unknown origin in 5); non-cirrhotic metabolic liver disease in 6 (citrullinemia in 3, OTCD in 2 and Crigler-Najjar syndrome type I in 1); biliary atresia in 7; primary biliary cirrhosis in 3; primary sclerosing cholangitis [PSC] in 2; Wilson's disease in 2; chronic hepatitis B in 2; autoimmune hepatitis in 1; Budd-Chiari syndrome in 1 and cryptogenic cirrhosis in 1. The follow-up period median was 83 months (range: 31–100 months).

Potential donors were evaluated by liver function tests, blood group, anatomical variation and graft size with computed tomography (CT) volumetry. All patients received grafts from family members. There were 14 male and 17 female donors with a median age of 43 years (range: 20–62 years) and a median weight of 57.3 kg (range: 39–81 kg). The indications for APOLT were: (i) fulminant hepatic failure in 6 patients; (ii) non-cirrhotic metabolic liver disease in 6 patients; (iii) small-for-size graft in 13 patients and (iv) ABO-incompatibility in 6 patients.

Surgical procedures

The operative procedure has been previously described (3,10). Native hepatectomy that varied in graft segment and volume, was performed prior to graft implantation. Graft types were left lateral segment in 8 cases, left lobe in 20 and right lobe in 3. The GRWR range was 0.45–2.08% (median 0.67%). The range of the operation time was 513–1379 min (median: 861 min), the range of the cold and warm ischemic time was 36–460 min (median: 157 min) and 32–77 min (median 48 min), respectively. Blood loss ranged 260–37650 g (median: 2645 g).

In one patient with biliary atresia, the left lateral segment of the native liver was prominently atrophic, and native hepatectomy was not necessary for graft implantation. The patient needed hepatic vein anastomosis with a new orifice of the inferior vena cava (11).

Part of the caudate lobe was resected in an initial 3 patients to shorten distance and to prevent kinking of the portal venous anastomosis. The stump of the native hepatic vein and hepatic artery was used for anastomosis. Twenty-five cases (80.6%) had diversion of the native portal vein to *prevent functional portal vein competition between the native and graft liver,* meaning that interruption of portal flow to the native liver with all portal flow going through the graft (3,12). Hepatic artery reconstruction was performed using the microvascular technique in all cases without using vascular grafts. Biliary reconstruction was achieved using Roux-en-Y hepaticojejunostomy.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids (13). Tacrolimus was begun 1 day prior to transplantation at a dose of 0.15 mg/kg/day divided into two doses, except for cases of hepatic encephalopathy and severe infection. The target for the post-transplantation whole blood trough concentration of tacrolimus was 10-12 ng/mL during the first 2 weeks and around 10 ng/mL thereafter. Steroids were started at graft reperfusion at a dose of 10 mg/kg, and then gradually reduced from 2 mg/kg/day to 0.3 mg/kg/day until the end of the first month. For patients receiving ABO-incompatible grafts, plasma exchange or double filtration plasmapheresis was performed to reduce anti-ABH antibody titers before transplantation. Post-operatively, prostaglandin E1, azathiopurine and additional steroids were administered (14).

Rejection

Acute cellular rejection was diagnosed with liver biopsy. Histological diagnosis and grading of acute rejection were performed according to the criteria proposed by Demetris et al. (15). All the rejection episodes were treated with a steroid bolus injection. Diagnosis of chronic rejection was based on internationally accepted histological criteria (16). Graft failure was defined as patient death or allograft removal regardless of the reason.

Statistical analysis

Values are presented as mean ± standard deviation. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan–Meier method and compared among groups with the Wilcoxon test. p-values of less than 0.01 were regarded as significant throughout the study.

The institutional review board approved the study and informed consent was obtained in all cases.

Results

APOLT was initiated between March 1995 and September 2001. In the same period we carried out 536 LDLTs. Thirty-one of 536 patients (5.8%) received APOLT (Table 5). None of the patients were lost to follow-up.

APOLT for fulminant hepatic failure (Table 1)

Six patients underwent APOLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was HBV in 1 patient and of unknown origin in 5. The median interval between onset of jaundice and encephalopathy was 42 days (range: 9–140 days). Coma grade at transplantation was grade III in 2 patients and grade IV in 4 patients. All patients necessitated pre-operative plasma exchange and continuous veno-venous hemodiafiltration therapy for progressive encephalopathy, coagulopathy and combined kidney/pulmonary dysfunction.