Table 2 Histological findings of the native liver, biopsy specimens and explanted liver

Patient no.	1	2	3	4	5	6	7
PBC staging of native livers							
Stage	4	4	4	4	4	4	2
Bile duct loss	3	3	3	3	3	2	1
Fibrosis	3	2	3	3	3	3	1
Orcein deposition	3	2	3	3	3	2	1
Hepatitis activities	1	1	1	0	0	1	1
Cholangitis activities	0	0	0	0	0	0	0
Needle biopsies	Congestion at 6 months	Suspected rPBC (duct loss and hepatitis) at 20 months	No biopsy	rPBC (cholangitis) and NASH at 71 months	rPBC (cholangitis and granuloma) and NASH at 90 months	No biopsy	ACR at 9 months
Main diagnosis	Outflow block	Chronic rejection	Chronic rejection	NASH	PVT and NASH	Chronic rejection	PVT
PBC recurrence	No	Mild (mild chronic cholangitis)	No	Mild (focal duct damage and portal fibrosis)	Mild (focal duct loss and portal inflammation)	No	No

ACR, acute cellular rejection; NASH, non-alcoholic steatohepatitis; PVT, portal vein thrombosis; rPBC, recurrence of PBC.

epithelioid granuloma; and (iv) bile duct damage according to Neuberger's criteria for the diagnosis of recurrent PBC based on liver histology.[15] In patient no. 2, biopsy showed (i) and (iv) (probable recurrence) and the explanted liver showed (i), (ii) and (iv) (definite recurrence); in no. 6, biopsy showed (i), (ii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence); and in no. 7, biopsy showed (i), (iii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence).

Case report of three patients with histological diagnoses of recurrent PBC

Patient no. 2 had refractory ACR requiring steroid pulse therapy on postoperative day (POD) 12, 36, 43, 97, 103, 420 and OKT3 monoclonal antibody on POD 434. Liver dysfunction associated with biliary dilatation developed 20 months after LDLT and we performed hepaticojejunostomy and wedge liver biopsy, which revealed suspected recurrence of PBC. Immunosuppression consisted of tacrolimus (3.0 mg/day), steroid (5 mg) and mizoribine (50 mg). Immunoglobulin M was 136, antimitochondrial antibody (AMA) 80 and anti-M2 152 mg/dL. Aggressive liver failure developed despite increased immunosuppression thereafter. She underwent retransplantation 24 months after LDLT.

In patient no. 4, alkaline phosphatase (ALP) began to increase 65 months after LDLT and liver dysfunction developed thereafter. Liver biopsy was performed 71 months after LDLT. Immunosuppression consisted of tacrolimus (2.0 mg/day) and steroid (5 mg). Aspartate aminotransferase (AST) was 44, ALP 432, γ-glutamyltransferase (γ-GT) 17, total bilirubin 1.7 mg/dL, AMA 80 and AMA-M2 155 mg/dL. Tacrolimus was changed to Neoral (Cyclosporine; Novartis, Basel, Switzerland), and mycophenolate mofetil (MMF) (2000 mg/day) was added. Ascites developed 1 year after and liver failure developed. She underwent retransplantation 88 months after LDLT.

In patient no. 5, liver dysfunction developed (AST, 82 IU/L; ALP, 685 IU/L) 50 months after LDLT and was successfully treated with steroid pulse therapy. Liver dysfunction developed and liver biopsy was performed 90 months after LDLT. Total bilirubin was 1.2 mg/dL, AST 57 IU/L, ALP 585 IU/L and γ-GT 48 IU/L. AMA and M2 were not measured. Immunosuppression consisted of tacrolimus only (4.0 mg/day), and MMF (2000 mg) was added thereafter. Portal hypertension started to develop. Radiological examinations yielded a diagnosis of artery-portal shunt of segment 3 of the graft. Shunt

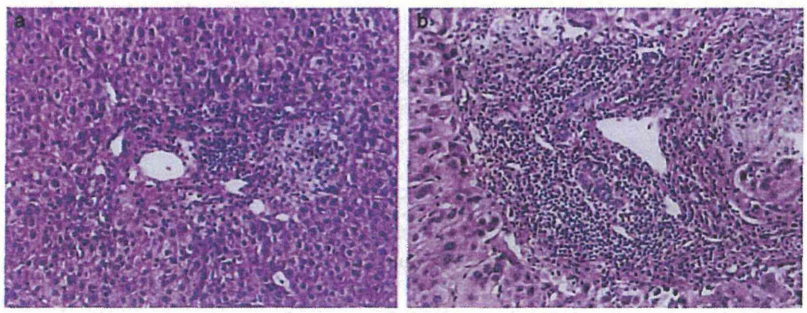

Figure 1 Histological findings of patient no. 2. (a) Wedge liver biopsy at postoperative month 20. Suspected recurrence of primary biliary cirrhosis (PBC) with bile duct loss and mild lobular and portal hepatitis. (b) Second explant liver (allograft). Suspected recurrence of PBC with moderate portal hepatitis and minimal bile duct damage (hematoxylin–eosin, original magnification ×200).

occlusion using metallic coils failed and led to liver failure. She underwent retransplantation 120 months after LDLT.

DISCUSSION

HISTOLOGICAL EXAMINATION IS the gold standard for recurrent PBC. Hubscher *et al.* reported the histological features to be mononuclear portal inflammation, portal lymphoid aggregate, portal granulomas and bile duct damage.[9] These findings are observed also in complications other than recurrent PBC. Lymphoid aggregate can be observed in chronic hepatitis, and bile duct damage and/or vanishing bile duct can be observed in chronic rejection or in the end stage of chronic cholangitis. Foamy cell arteriopathy, which is another specific feature of chronic rejection, is seldom observed on needle biopsy. Duct loss without portal granuloma suggests chronic rejection. The current study focusing on explanted allografts was conducted to avoid these uncertain factors.

Recently, late cellular rejection, chronic hepatitis, and de novo autoimmune hepatitis were discussed as causes of late liver allograft dysfunction.[16] Haga *et al.* reported perivenular lymphoplasmacytic infiltration in a case of their series, which simulated autoimmune hepatitis rather than typical PBC. In our series, ANA was strongly positive prior to primary transplantation in two patients but there were no such findings.

The incidence of recurrent PBC increased along with long-term follow up. Montano-Loza *et al.* studied the cumulative probability of PBC recurrence after LT.[17] Their histological study was not based on protocol biopsy. The overall 5- and 10-year probability of recurrence was 13% and 29%, respectively, in their series. They analyzed risk factors for recurrence and the clinical impacts. Although PBC transplant recipients receiving cyclosporin have a lower risk of disease recurrence, the development of recurrent PBC had no impact on long-term patient survival during 10 years of follow up. The incidence in LDLT based on protocol biopsy was 40% during 10 years of follow up.[3] Besides the increasing incidence, progression of recurrent PBC is still a concern, although progression of recurrent PBC was slow within 10 years of follow up in our series. In Japanese registries of LT, some cases of mortality after 10 years have been reported but information about their causes is not available.[18] A precise study of these cases is required to reveal the risks including recurrence in long-term follow-up.

Protocol biopsies for early diagnosis of recurrent PBC may not be essential to improve clinical courses of

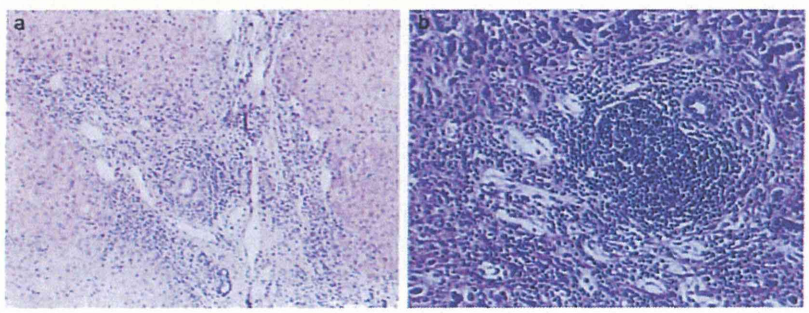

Figure 2 Histological findings of patient no. 4. (a) Needle liver biopsy at postoperative month 71. Recurrence of primary biliary cirrhosis (PBC) with non-suppurative cholangitis and moderate portal hepatitis and fibrosis. (b) Second explant liver (allograft). Suspected recurrence of PBC with focal duct damage and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×150; [b] ×200).

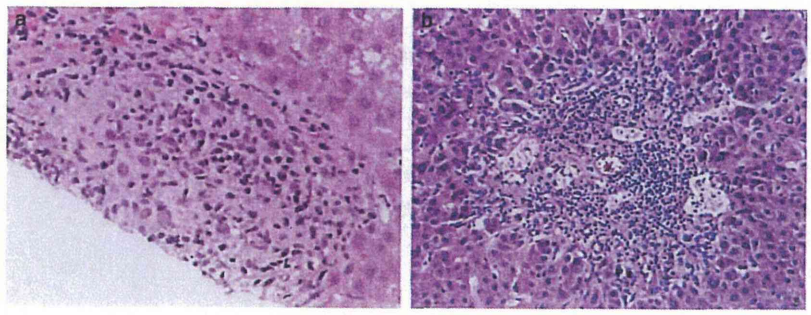

Figure 3 Histological findings of patient no. 5. (a) Needle liver biopsy at postoperative month 90. Recurrence of primary biliary cirrhosis (PBC) with focal cholangitis and epithelioid granuloma. (b) Second explant liver (allograft). Suspected recurrence of PBC with bile duct loss and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×250; [b] ×200).

patients after LT for PBC. Timely biopsies and suitable radiological examinations, when hepatic chemistries deteriorate, are important to improve the clinical course within 10 years after transplantation.

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ORIGINAL ARTICLE

The Outcomes of Patients with Severe Hyperbilirubinemia Following Living Donor Liver Transplantation

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Abstract
Background Prolonged hyperbilirubinemia (HB) following living donor liver transplantation (LDLT) can be a risk factor for early graft loss and mortality. However, some recipients who present with postoperative hyperbilirubinemia do recover and maintain a good liver function.
Aim The purpose of this study was to investigate the risk factors for hyperbilirubinemia following LDLT and to identify predictors of the outcomes in patients with post-transplant hyperbilirubinemia.
Methods A total of 107 consecutive adults who underwent LDLT in Nagasaki University Hospital were investigated retrospectively. The patients were divided into two groups according to postoperative peak serum bilirubin level (HB group: ≥30 mg/dl; non-HB group: <30 mg/dl). These two groups of patients and the prognosis of patients in the HB group were analyzed using several parameters.
Results Seventeen patients (15.9 %) presented with hyperbilirubinemia, and their overall survival was significantly worse than patients in the non-HB group ($n = 90$). Donor age was significantly higher in the HB group ($P < 0.05$). Of the 17 patients in the HB group, nine survived. The postoperative serum prothrombin level at the time when the serum bilirubin level was >30 mg/dl was significantly higher in surviving patients ($P < 0.01$).
Conclusions The use of a partial liver graft from an aged donor is a significant risk factor for severe hyperbilirubinemia and a poorer outcome. However, those patients who maintain their liver synthetic function while suffering from hyperbilirubinemia may recover from hyperbilirubinemia and eventually achieve good liver function, thus resulting in a favorable survival.

Keywords Living donor liver transplantation · Hyperbilirubinemia · Partial graft · Small-for-size graft syndrome · Acute cellular rejection

Introduction

Hyperbilirubinemia following living donor liver transplantation (LDLT) can be caused by several mechanisms, such as initial poor function, acute cellular rejection, surgical complications, small-for-size syndrome, drug toxicity, among others. Hyperbilirubinemia has also been reported to be a risk factor for early graft loss and mortality [ ]. However, some recipients can overcome hyperbilirubinemia, and these patients subsequently achieve and maintain a good liver function after their eventual recovery from hyperbilirubinemia. The aim of this study was to retrospectively clarify the risk factors for the development of postoperative severe hyperbilirubinemia and to identify any predictors for the outcomes in patients who present with hyperbilirubinemia following LDLT.

Patients and Methods

We retrospectively analyzed the data of 107 consecutive adult patients (67 males, 40 females, median age 55 years, age range 16–68 years) who underwent LDLT in the Department of Surgery of Nagasaki University Hospital between November 1997 and January 2010. The etiologies

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of the liver disease were hepatitis C virus infection (35 patients), hepatitis B virus infection (25 patients), non-viral causes (40 patients), and fulminant liver failure (7 patients) (Table). During this period, we occasionally treated patients with a postoperative bilirubin level of >20 mg/dl. Marubashi et al. [ ] reported that a postoperative peak serum bilirubin level of >27 mg/dl could be a predictor of short-term graft outcome. Therefore, we defined those patients who had presented with a postoperative peak serum bilirubin level of >30 mg/dl as having hyperbilirubinemia (HB group); the remaining patients formed the non-HB group.

The two groups of patients were compared for preoperative serum bilirubin level; donor age; the postoperative peak alanine aminotransferase (ALT); model for end-stage liver disease (MELD) score; graft weight (GW)/standard liver volume ratio [SLV; SLV (ml) = 706.2 × body surface area (m^2) + 2.4] [ ]; type of graft; development of acute cellular rejection [as proven by biopsy within postoperative day (POD) 60]; ABO compatibility; the development of biliary complications. We defined a biliary complication as anastomotic stenosis that needed interventions by means of balloon dilatation, stent placement, or re-operation. We divided the types of grafts into those for the right lobe and left lobe, respectively. The right lobe included the right lateral sector, and the left lobe included the left lateral segment.

In the HB group, we compared surviving and non-surviving patients for all of the above-mentioned parameters as well as for serum prothrombin [PT (%)] and creatinine levels at the time when the serum bilirubin level was >30 mg/dl. In the HB group, no patients received administration of fresh frozen plasma at the time of diagnosis. We used log-rank test for survival comparison. Group data were compared with the Mann–Whitney *U* test, and differences between proportions of categorical data were compared with the χ^2 test. Furthermore, several factors detected in the univariate analysis with *P* values of <0.15 were entered into a multivariate analysis. We used multivariate logistic regression analysis for the multivariate analysis. A *P* value <0.05 was considered to be statistically significant.

Table 1 Indication for liver transplantation

Cause of liver disease	Total ($n = 107$)	HB group ($n = 17$)	Non-HB group ($n = 90$)
Liver cirrhosis (hepatitis virus C)	35	6	29
Liver cirrhosis (hepatitis virus B)	25	4	21
Alcoholism	11	2	9
Primary biliary cirrhosis	8	3	5
Fulminant hepatitis	7	0	7
Liver cirrhosis (non-B non-C)	6	0	6
Primary sclerosing cholangitis	3	0	3
Budd–Chiari syndrome	1	0	1
Caroli's disease	1	0	1
Graft failure	4	2	2
Others	6	0	6

HB Hyperbilirubinemia

Results

Of the 107 consecutive adult patients who underwent LDLT at our hospital during the study period, 17 (15.9 %) met our criteria for HB and were included in the HB group; the remaining 90 patients (84.1 %) formed to the non-HB group. The overall survival rate was significantly different between the groups ($P < 0.01$) (Fig.). Time-zero biopsies showed no apparent differences between patients in the HB and non-HB group. Protocol biopsy was not performed postoperatively except in cases of cellular rejection or recurrence of hepatitis was suspected. The median donor age was significantly higher in the HB versus the non-HB group [50 (range 22–63) vs. 36 (19–67) years, respectively; $P < 0.05$], and ABO incompatibility was identified as a risk factor for posttransplant hyperbilirubinemia. The median preoperative serum bilirubin level tended to be higher in the HB group than in the non-HB group [5.4 (range 1.1–39.5) vs. 3.3 (0.6–42.7) mg/dl, respectively; $P = 0.06$]. The median postoperative peak ALT level was significantly higher in the HB group than in the non-HB group [569 (range 120–1,907) vs. 339 (79–3,359) IU/l,

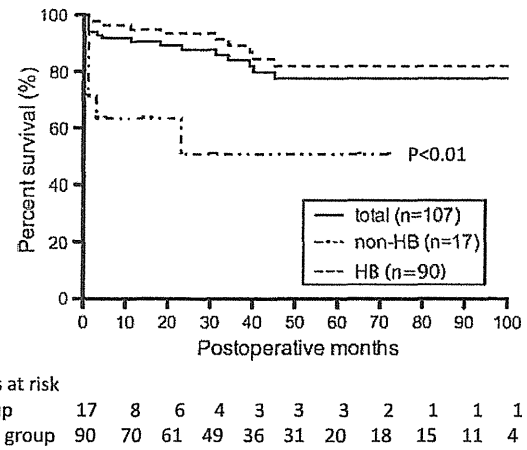

Fig. 1 Kaplan–Meier curves of the postoperative survival of patients with hyperbilirubinemia (*HB* group) and without hyperbilirubinemia (*non-HB* group)

Table 2 Analysis of predictive factors for hyperbilirubinemia (univariate analysis)

Predictive factors	HB group[a] ($n = 17$)		Non-HB group[a] ($n = 90$)		P value
GW/SLV (%)	39.9 (24.9–56.3)		44.1 (23.6–85.3)		0.139
Donor age (years)	50 (22–63)		36 (19–67)		0.035
MELD score	22 (9–32)		18 (7–40)		0.217
Preoperative serum total bilirubin (mg/dl)	5.4 (1.1–39.5)		3.3 (0.6–42.7)		0.061
postoperative peak ALT(IU/l)	569 (120–1,907)		339 (79–3,359)		0.02
	+ (n)	%	+ (n)	%	
Acute cellular rejection (<POD 60)	5/17	29	26/90	29	0.804
Biliary complication	0/17	0	18/90	20	0.07
Type of graft					
Right lobe	10/17	59	36/90	40	
Left lobe	7/17	41	54/90	60	0.241
ABO incompatibility	6/17	35	9/90	10	0.01

GW/SLV Graft weight/standard liver volume ratio, *MELD* model for end-stage liver disease, *POD* postoperative days, *ALT* alanine aminotransferase

[a] Values are presented as the median with the range in parenthesis

Table 3 Multivariate analysis of postoperative hyperbilirubinemia

Preoperative risk factors	Yes/no	P value
GW/SLV (%)	–	0.107
Donor age (years)	–	0.0125
Preoperative serum total bilirubin (mg/dl)	–	0.032
ABO incompatibility	Yes	0.163

respectively; $P = 0.02$]. There were no significant differences in the GW/SLV, MELD score, type of graft, and incidence of biliary complication and acute cellular rejection between the groups (Table). The multivariate logistic analysis identified donor age ($P = 0.0125$) and preoperative serum bilirubin level ($P = 0.032$) as preoperative risk factors for postoperative hyperbilirubinemia (Table).

Of the 17 patients in the HB group, nine were alive at the writing of this manuscript. The results of the comparison between surviving and non-surviving patients are shown in Table . The median postoperative PT (%) at the time when the serum bilirubin level was >30 mg/dl was significantly higher in surviving patients than in those that did not survive [52 (range 26–59) vs. 33.5 (20–60) %, respectively; $P < 0.01$]. The median postoperative serum creatinine level at the time when the serum bilirubin level exceeded 30 mg/dl tended to be lower in surviving patients than in those that had not survived [1.2 (range 0.5–2.9) vs. 1.86 (0.4–3.1) mg/dl, respectively; $P = 0.06$]. There were no significant differences between surviving patients and non-surviving patients for donor age, GW/SLV, preoperative serum bilirubin level, MELD score, postoperative duration when the serum bilirubin level was >30 mg/dl, ABO incompatibilty, and acute cellular rejection (Table). The multivariate logistic analysis was not performed because of the small number of patients. Table summarizes the characteristics and the postoperative course of patients in the HB group. Eight patients did not survive—one patient due to severe acute cellular rejection and seven patients due to infection. The indications for liver transplantation for non-surviviors were liver cirrhosis (hepatitis C virus; 3 patients), primary biliary cirrhosis (3 patients), (hepatitis B virus; 1 patient), and graft failure (1 patients) (Table). None of these patients had suffered from short-term recurrence of viral hepatitis and hepatocellular carcinoma after transplantation. One patient (Table , case no. 10) was considered to be small-for-size syndrome with massive ascites and prolonged hyperbilirubinemia without arterial or portal occlusion and rejection. However, she had maintained PT (%) and survived. Although postoperative biopsies were performed for 11 patients in the HB group, no specific causes of hyperbilirubinemia were detected besides the findings of acute cellular rejection or recurrent hepatitis.

Discussion

In this study, we analyzed the risk factors for postoperative HB and the prognosis of patients who belonged to the HB group. Our results indicate that the donor age was most strongly correlated with the development of HB. A multivariate analysis also identified donor age and patient preoperative total bilirubin level as significant risk factors for post-transplant HB. The outcome of liver transplantation from aged donors is controversial. Some studies have shown that the outcomes of using grafts from donors older than 50 years without additional risk factors are similar to those of using grafts from donors younger than 50 years [,]. However, the data from a registry of the Japanese Liver Transplantation Society show that patients who received a graft from an older donor had a significantly

Table 4 Comparison of risk factors for mortality in HB group (univariate analysis)

Risk factors	Surviving group[a] ($n = 9$)		Non-surviving group[a] ($n = 8$)		P value
GW/SLV(%)	40 (24.9–56.3)		39.2 (26.9–48.4)		0.847
Donor age	50 (22–61)		50.5 (22–63)		0.847
MELD score	22 (13–32)		22 (9–40)		1
Preoperative total bilirubin (mg/dl)	3.2 (1.9–39.5)		14.2 (1.1–28.7)		0.289
Timing of diagnosing HB	19 (5–28)		17 (6–32)		0.885
Prothrombin time (%) at HB diagnosis	52 (26–59)		33.5 (20–60)		0.004
Serum creatinine (mg/dl) at HB diagnosis	1.2 (0.5–2.9)		1.86 (0.4–3.1)		0.067
	+ (*n*)	%	+ (*n*)	%	
ABO incompatibility	3/9	33	3/8	38	1
Acute cellular rejection (<POD 60)	2/9	22	3/8	38	0.619

[a] Values are presented as the median with the range in parenthesis

Table 5 Characteristics and postoperative courses of patients in HB group

Case no.	Gender	Age	Indication for transplantation	ABO incompatibility	GW/SLV	Timing of diagnosing HB	Prothrombin (%) at HB diagnosis[a]	Outcomes	Cause of death
1	Male	63	B-LC, HCC	+	36.9	36	45	Dead	Infection
2	Female	61	PBC	+	26.9	26	25	Dead	Infection
3	Female	61	C-LC, HCC	–	43.6	12	29	Dead	Infection
4	Female	62	PBC	–	38.4	45	31	Dead	Infection
5	Male	57	C-LC, HCC	–	40	18	37	Dead	Infection
6	Male	57	C-LC, HCC	–	48.4	15	36	Dead	Infection
7	Male	41	PBC	–	44.6	16	31	Dead	ACR
8	Female	56	Graft failure	+	36.3	14	43	Dead	Infection
9	Female	54	C-LC, HCC	+	41.2	28	61	Alive	
10	Female	59	C-LC, HCC	–	24.9	26	45	Alive	
11	Male	58	B-LC, HCC	–	29.7	17	46	Alive	
12	Male	56	B-LC, HCC	–	44.2	37	76	Alive	
13	Female	53	C-LC	+	40	11	55	Alive	
14	Male	22	Graft failure	–	56.3	5	41	Alive	
15	Male	52	B-LC, HCC	+	36.1	34	52	Alive	
16	Male	62	Alcoholism	–	43.5	19	60	Alive	
17	Female	46	Alcoholism	–	37.8	17	34	Alive	

C-LC Liver cirrhosis type C, *B-LC* liver cirrhosis type B, *PBC* primry biliary cirrhosis, *ACR* acute cellular rejection

[a] At the time when the serum bilirubin level was >30 mg/dl

worse survival [5]. Notable findings of two studies which investigated non-transplanted aged livers were: 40 and 50 % decreases in vascular inflow and biliary flow, respectively, impairment of energy- and microtubule-dependent transport processes, with reduced endoplasmic reticulum mass, cumulative pigmented waste deposition, and a reduced ability to scavenge reactive oxygen intermediates [6, 7].

It has been reported that patients who receive a graft from an aged donor tend to have a greater incidence of delayed graft function [8, 9]. A multivariate analysis also revealed that the use of these grafts is associated with an increased incidence of recurrent hepatitis C [10]. A relative poorer regeneration of the liver graft from an aged donor has also been reported [11]. Taken together, these findings indicate that clinicians should be aware that the use of grafts from aged donors could lead to the development of severe hyperbilirubinemia by a multifactorial mechanism.

The HB group included significantly more patients who had undergone ABO blood type-incompatible LDLT. The outcomes of ABO blood type-incompatible LDLT have improved over the years, and many institutes have adopted ABO-incompatible LDLT owing to the various treatments that can be used to overcome antibody-mediated rejection (AMR). AMR is the result of a circulatory disturbance that is caused by injury to the endothelium due to an antibody–

antigen–complement reaction. The typical clinical manifestations of AMR are hepatic necrosis and intrahepatic biliary complications [12]. Although no patients in our study had developed hepatic necrosis or apparent intrahepatic biliary complications with the prophylaxis, including rituximab and plasma exchange, our results suggest that patients undergoing ABO-incompatible LDLT may have a greater chance of developing postoperative severe hyperbilirubinemia.

The prognosis of the HB group was significantly worse than that of the non-HB group. Marubashi et al. [1] reported devastating outcomes in patients with a postoperative peak serum bilirubin level of >27 mg/dl, with eight of their grafts resulting in early graft loss within 1 year. In contrast, we experienced a number of patients with severe hyperbilirubinemia post-LDLT who eventually recovered their liver function; in fact, nine of the 17 patients in the HB group survived. Therefore, we investigated the perioperative parameters to clarify the risk factors for decreased survival. Our analysis revealed that the postoperative PT (%) at the time when the serum bilirubin level exceeded 30 mg/dl for the first time was significantly correlated with the prognosis based on the univariate analyses. Based on these results, the patients who were able to maintain their liver synthesis function were able to recover their liver function despite a temporal deterioration in bilirubin excretion.

Cholestasis has been recognized as a clinical manifestation of small-for-size graft syndrome, and the improvement of temporal cholestasis in proportion to the liver regeneration can be expected in cases of partial liver graft transplantation. We tried to exclude small-for-size syndrome with massive ascites. Although there is no consensus on the definition of small-for-size syndrome, there was one patient in the HB group who was suspected to have small-for-size syndrome, and she recovered spontaneously [normal range PT (%)] [13, 14]. In fact, GW/SLV was not a significant risk factor for the development of hyperbilirubinemia in our present study.

In addition, the postoperative serum creatinine level at the time when the serum bilirubin level exceeded 30 mg/dl for the first time tended to be lower in surviving patients. Acute kidney injury following liver transplantation has been reported to be associated with a worse outcome [15]. It is not hard to comprehend that HB patients with multiple organ dysfunction would have be a worse prognosis.

In conclusion, the use of a partial liver graft from an aged donor is considered to be a significant risk factor for postoperative severe hyperbilirubinemia. Although the outcomes of the HB patients were worse than those for the non-HB group, we should recognize that recovery is possible even from severe hyperbilirubinemia in those patients who are able to maintain their liver synthetic function during the postoperative course.

Conflict of interest None.

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EDITORIAL

Is low central venous pressure effective for postoperative care after liver transplantation?

Susumu Eguchi

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The central venous pressure (CVP) has been regarded as an important factor for reducing blood loss and the blood transfusion rate during major hepatectomy, and can be controlled by positive end-expiratory pressure (PEEP) or certain drugs and the optimal positioning of the patient [1–4].

In this issue of *Surgery Today*, Wang et al. [5] describe the beneficial effects of lowering the CVP for achieving a better postoperative outcome compared with conventional fluid management in deceased donor liver transplantation based on a prospective randomized controlled study. They report that the low CVP group showed (1) less intraoperative blood loss, (2) a decreased need for intraoperative blood transfusion, (3) fewer lung-related complications at 1 month postoperatively, (4) a shorter intubation period and (5) equal patient survival at 1 year after liver transplantation. A previous retrospective study showed intraoperative blood transfusion to be a risk factor for postoperative lung complications [6]. The present study was done in a prospective, randomized manner, which yielded the same results as those seen in the previous retrospective study. The methods used to reduce the CVP in the present study were the use of the Fowler position, fluid restriction and drugs (e.g., nitroglycerin, furosemide and somatostatin). These methods have also been used in previous studies to reduce the intraoperative CVP, and therefore they appear to be valid for this kind of study [2].

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Although the results provided in the article were of high importance, lowering the CVP during liver transplantation might still be controversial and may have ambivalent aspects with regard to the lack of a relationship between the early complication rates, including renal, hepatic and pulmonary complications, and the CVP following liver transplantation [7–10]. For example, apart from the reduced pulmonary complication rate, and the lower blood loss and blood transfusion rate, what would be the influence of lowering the CVP on the postoperative care following liver transplantation? If blood product administration during the intensive care period is increased, then the policy to limit CVP during surgery would be in vain. Therefore, the readers will also want to know: How would the perfusion in the organ be affected? How would the lactate level in the blood after LT be affected, not only at the end of surgery but also during the postoperative period? How would the post-transplant blood product requirements be affected?

In fact, the period in which the CVP is lowered may be of importance. For example, Feng et al. [7] reported that a low CVP during the pre-anhepatic phase reduced the intraoperative blood loss, protected the liver function and it also had no detrimental effects on the renal function after LT. On the other hand, Cywinski et al. reported that a low CVP during the post-anhepatic phase was not associated with any benefit in terms of immediate postoperative allograft function, graft survival or patient survival [10]. In addition, the cut-off value for CVP monitoring in previous studies varied between 5 and 10 mmHg.

We therefore await further reports from other investigators before drawing any definitive conclusions about the above-mentioned issues, since liver transplant surgery, especially partial liver transplantation, is often affected by multiple factors [11].

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Clinical Transplantation

Self-assessment of postoperative scars in living liver donors

Imamura H, Soyama A, Takatsuki M, Muraoka I, Hara T, Yamaguchi I, Tanaka T, Kinoshita A, Kuroki T, Eguchi S. Self-assessment of postoperative scars in living liver donors.

Abstract: Background: The application of less invasive techniques for liver surgery in patients undergoing living donor hepatectomy (LDH) has been reported. The objective of this study was to evaluate physical status according to type of incision in donors.
Methods: One hundred and forty-seven living liver donors underwent hepatectomy using three types of incisions: (i) Mercedes-Benz incision (M.B.), (ii) right subcostal incision with midline up to xiphoid incision (S.C.), and (iii) short upper midline incision (U.M.). A total of 100 donors answered the questionnaires, and 87 had sufficient data for the analyses. An original questionnaire designed to evaluate the physical status concerning postoperative scars. The questionnaire consisted of three major categories: appearance, sensation, and daily activities. The univariate analysis was performed using the chi-square test.
Results: Numbness of the abdominal wall was reported more frequently by the donor with M.B.s and right subcostal incisions up to xiphoid incisions. In terms of appearance, sensation, and daily activities, LDH with a U.M. was found to have a good self-assessment compared with that performed using other types of incisions.
Conclusions: LDH with a U.M. is a preferable procedure in terms of physical status and safety.

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Key words: body image – living donor liver transplantation – questionnaire – self-assessment – upper midline incision

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Liver transplantation is the only life-saving intervention for patients with end-stage liver disease. Donors who participate in living donor liver transplantation (LDLT) are typically healthy adults who do not receive any medical benefits from the procedure themselves. LDLT donors face surgical risks, including serious morbidity and mortality in some reported cases. Therefore, liver transplant surgeons must prioritize the safety and well being of donors.

Recently, the application of less invasive techniques for liver surgery during living donor hepatectomy (LDH) has been reported (1–3). We previously reported that less invasive surgery is effective in terms of reducing abdominal wall morbidity and improving postsurgical recovery. In our technique, we begin the LDH procedure with a Mercedes-Benz incision (M.B.), then change to a right subcostal incision up to a xiphoid incision. At present, we have adopted a hybrid technique through a short upper midline incision (U.M.) (4).

When performing LDLT, the safety of donors is of the utmost importance. Any type of morbidity can affect donors, both physically and psychologically. The postoperative quality of life of living liver donors has been investigated using SF-36 and SF-12 questionnaires (5, 6); however, Parikh et al. (7) reported that the conventional QOL instruments that have primarily been used, such as the SF-36 and SF-12, may not adequately assess the QOL in LDLT donors.

Also, some reports evaluating postoperative scars have been published. Body image questionnaires have been previously described and applied

in the evaluation of scars after appendectomy, nephrectomy, and ileocolic resection (8–10). With regard to LDH, Dubay et al. (5) reported the impact on the cosmesis and body image using body image questionnaires and the SF-36.

The aim of this study was to evaluate the physical status according to the type of incision in donors who had undergone LDH. We developed an original questionnaire by modifying previously reported questionnaires concerning postoperative scars, which focused on appearance, sensation, and daily life activities associated with postoperative scars.

Donors and methods

Between August 1997 and September 2011, 147 patients underwent LDLT at Nagasaki University Hospital. During this period, we performed LDH using three types of incisions (Fig. 1): (i) M.B. 1997–2005, (ii) right subcostal incisions up to xiphoid incisions (S.C. 2005–2010), and (iii) U.M. 2010-present (4).

There were no operation-related mortalities in the living donors. One hundred donors answered the questionnaires (68% of the total number of donors), and 87 (59% of the total number of donors) had sufficient data to analyze (Table 1). The details were as follows: M.B. = 47/88 (53%), S.C. = 31/44 (70%), and U.M. = 9/15 (60%). The median and range of the follow-up duration in each group were as follows: M.B.: 86 months (47–181), S.C.: 21 months (20–58), and U.M.: 10.5 months (13–26).

We conducted a cross-sectional study using an original questionnaire that focused on physical status associated with postoperative scars. The questionnaire was simultaneously sent to all donors by mail. The questionnaire consisted of three issues: (i) appearance (length, color, surface, impression), (ii) sensation (pain, stretching, stiffness, numbness, touch, and temperature sensation), and (iii) daily life (posture problems, resistance to exposing the scar, obstacles created by the scar, referred pain). The subjects were requested to answer a questionnaire regarding the LDH incision. There were no donors who had undergone a recent operation or who had clinical symptoms at the first medical examination.

Statistical analysis

The univariate analysis was performed using the chi-square test. p values < 0.05 were considered to be significant.

Results

Appearance of the scar

In the U.M. group, donors reported that their incisions were either short (n = 3) or as expected (n = 6) compared with their image before surgery (p = 0.03, Fig. 2). Regarding scar color, 33% of the donors in the U.M. group did not feel discomfort. In the S.C. and M.B. groups, 45% and 53%, respectively, of the donors answered similarly (p = 0.73). Regarding scar appearance, 30% of the donors in each group reported that they did not feel discomfort or sense irregularities in the surface of their scar (p = 0.87). Seventy-seven percent of the donors in the U.M. group were satisfied with the appearance of their scar, compared with 40% of the donors in the M.B. group and 35% of the donors in the S.C. group (p = 0.12).

Sensation in the abdomen

In all groups, some of the donors reported current continuous pain. The area of pain was located around their scar. In the M.B. group, 42% of the donors reported continuous pain, even during the long median follow-up period (p = 0.15, Fig. 3). The rate of numbness was 30% (n = 14) in the

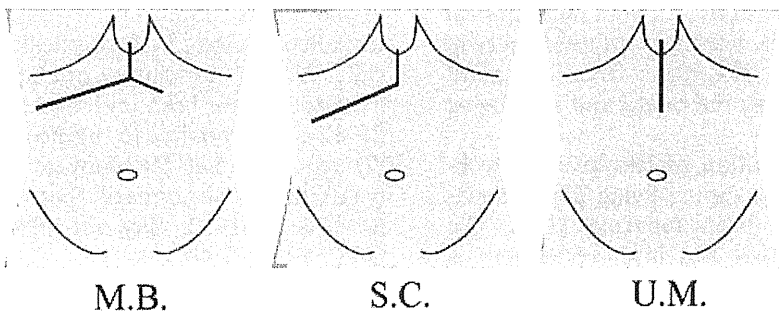

Fig. 1. The diagrams show the three types of incisions. From the left, M.B., Mercedes-Benz incision, S.C., right subcostal incision with midline up to xiphoid incision, U.M., short upper midline incision.

Table 1. Demographic characteristics of the living liver donors (number = 87)

Characteristics	M.B. (Total number = 47)	S.C. (Total number = 31)	U.M. (Total number = 9)
Age (yr), mean ± SD	42 ± 12	40 ± 14	46 ± 10
Gender (M:F)	21:26	20:11	4:5
Relationship to recipient			
First-degree relative	26	17	5
Non-first-degree relative	12	7	2
Spouse	8	7	2
Other (including anonymous)	1	0	0
Graft type			
Right lobe	29	11	3
Extended left lobe	18	20	6
Recipient outcome	12 deaths	5 deaths	2 deaths

M.B., Mercedes-Benz incision group; S.C., right subcostal incision with extension up to xiphoid incision group; U.M., short upper midline incision group.

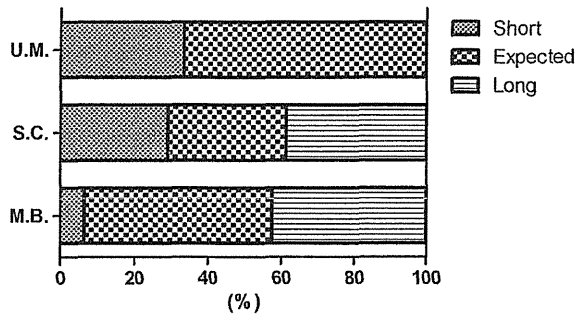

Fig. 2. The details of 1.a. (How do you feel about the length of your postoperative scar compared with the image you had before surgery?). The shorter the total length of incisions became the rate of "shorter" or "as expected" increased. In the upper midline incision group, the donors tended to consider the scar shorter than expected before surgery.

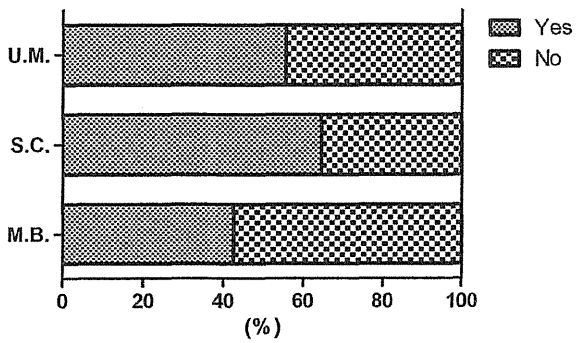

Fig. 3. The details of 2.a. (Do you currently feel pain?). In all groups, some of the donors reported current continuous pain. The area of pain was present around their scar. In the Mercedes-Benz incision group, 42% of the donors reported continuous pain even 168 months after the operation.

M.B. group and 29% (n = 9) in the S.C. group, whereas only one donor in the U.M. group (11%) reported numbness (p = 0.50, Fig. 4). The area of numbness was present in the right subcostal incision and part of the region up to the xiphoid

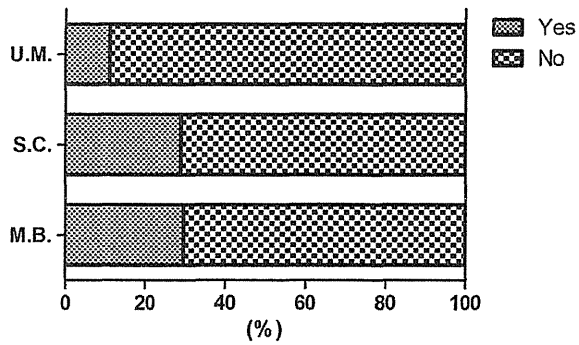

Fig. 4. The details of 2.c. (Do you feel numbness around the scar?). The rate of numbness was 30% (n = 14) in the Mercedes-Benz incision group and 29% (n = 9) in the right subcostal incision with midline up to xiphoid incision group, whereas only one donor in the short upper midline incision group (11%) reported numbness (p = 0.50). The area of numbness was present at the right subcostal incision and a part of the region up to the xiphoid incision.

incisions. As to tactile and temperature sensation, a loss of cutaneous sensation was observed in 47% of the donors in the M.B. group (n = 22), 39% of the donors in the S.C. group (n = 12), and 22% of the donors in the U.M. group (n = 2) (p = 0.36, Fig. 5). An area of missing sensation was concentrated around right subcostal incisions.

Activities of daily life

Forty-four percent of the donors in the U.M. group reported posture problems, a rate that was higher than that observed in the M.B. (14%) and S.C. (23%) groups (p = 0.12). A described example was in the case of bending forward to put on their shoes. Many donors reported feeling discomfort about exposing their scar: 62%, 65%, and 67% in the M.B., S.C., and U.M. groups, respectively (p = 0.94).

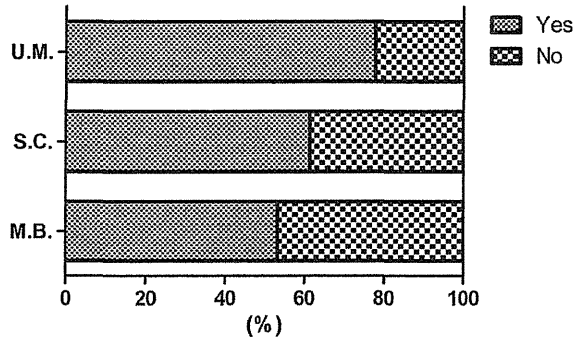

Fig. 5. The details of 2.d. (Do you have tactile and temperature sensation in the abdomen?). A loss of cutaneous sensation was observed in 47% of the donors in the Mercedes-Benz incision group (n = 22), 39% of the donors in the right subcostal incision with midline up to xiphoid incision group (n = 12), and 22% of the donors in the short upper midline incision group (n = 2). The area of missing sensation was concentrated around right subcostal incisions.

Fifty-six percent of the donors in the U.M. group reported that they experienced obstacles caused by their scar when they returned to their daily lives. In the M.B. and S.C. groups, 30% and 45% reported experiencing obstacles, respectively ($p = 0.34$). Regarding referred pain, 11% of the donors in the U.M. group reported pain ($p = 0.93$). The details of the scar sites were not described by the donors with referred pain in the U.M. donor group. The majority (89%) of the donors in the U.M. group were currently satisfied with their scar in daily life (Fig. 6).

Through this questionnaire, statements about abdominal incisional hernias were recognized for two donors, who had undergone M.B. and S.C. incisions.

Detailed descriptions in the free writing space revealed some problems with regard to the social or psychological status of the subjects. Some donors were worried about the appearance of the scar, for example, in the case of public spas. In terms of the psychological aspects, one donor described anxiety about scar and suffered from negative memories of the operation.

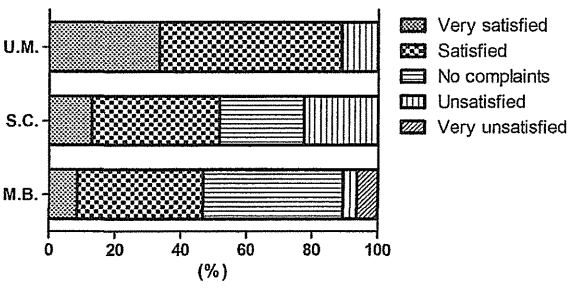

Fig. 6. The details of 3.e. (How satisfied are you with your scar in daily life?). Current evaluation of the scars in daily life. Eighty-nine percent of the donors in the short upper midline incision group were currently satisfied with their scars.

Discussion

This study revealed that the grade of satisfaction and symptoms experienced among LDLT donors differ according to the type of incision used during surgery.

To the best of our knowledge, this is the first report to examine self-evaluations of postoperative scars in living liver donors. Postoperative scars are one of the most important factors determining postoperative clinical course in donors. Experiencing a good healing process and having a scar in good condition can provide donors physical satisfaction.

M.B.s and right subcostal incisions up to xiphoid incisions contain a right subcostal component. This is an essential and inevitable part of LDH. Subcostal incisions divide the abdominal muscles and the ventral rami of the intercostal nerves, invariably dividing T8 and T9. This causes numbness in the area below the subcostal incision. Jain et al. (11) reported that abdominal wall numbness was observed in 100% of recipients who underwent liver transplantation during up to eight yr of follow-up, and 5% of patients experienced cutaneous complications from thermal burns or blunt trauma. In our cases, numbness was revealed in 30% (n = 14) of the subjects in the M.B. group and 29% (n = 9) in the S.C. group, both of which have a right subcostal component.

Our findings revealed that donors often experience continuous pain, numbness, and loss of cutaneous sensation. Some donors continued to suffer from these symptoms even during long postoperative periods. The longest case was assessed 10 yr after the donation. In particular, the donors reported that the right subcostal portion of their scars tended to be symptomatic. In previous reports, the physical condition was demonstrated to decrease immediately after donation, but returned to the postoperative level within one yr based on the SF-36 or SF-12 (12, 13). The differences in the present results and the previous studies suggest that conventional QOL instruments cannot sufficiently evaluate the physical status of LDLT donors.

In contrast, the donors with upper midline incisions obtained better cosmesis and good results in terms of scar length, numbness, and cutaneous sensation compared with the donors with M.B.s or right subcostal incisions up to xiphoid incisions. This is because LDH performed through a U.M. can avoid muscle disruption and division of the

ventral rami of the intercostal nerves. Donors in the U.M. group should be observed continuously due to the short median follow-up duration. In addition to preventing donors from developing scar complications, U.M.s are considered to contribute to maintaining a good postoperative course with respect to physical status.

The U.M. group reported better impressions of their scars in daily life compared with the other groups. Good postoperative courses and favorable wound healing may have been related to these results. In the early postoperative period, the lack of muscle disruption enables donors with U.M.s to achieve to early ambulation and rehabilitation. This reduces the physical burden imposed on the donors. In addition, the impression of a short scar length reassures these donors in terms of their postoperative daily life. We think that postoperative scars are a kind of symbol of the recovery process and that the condition of a scar often affects the postoperative course of donors. Also, some donors reported that they recollected undesired results regarding the recipients when they saw their scars. Physicians should be aware of the meaning of postoperative scars and care for the donor's feelings.

This study was preliminary because of the small sample sizes and short follow-up periods regarding U.M.s. However, we foresee that using a less invasive procedure, including the U.M., may reduce the physical burden for donation. It would also bring about a speedier recovering to daily life for donors.

In conclusion, LDH performed through a U.M. is considered to contribute to reducing the rate of scar-related complications and improving satisfaction in physical status compared with that performed with other types of incisions.

Details of the original questionnaire

1. Appearance of the scar
   a. How do you feel about the length of your postoperative scar compared to the image you had before surgery?
      (Short-Expected-Long)
   b. Are you satisfied with the color of the skin around the scar?
      (Yes, extremely-A little bit-No, not at all)
   c. Are you satisfied with the proportion of the surface of the scar?
      (Yes, extremely-A little bit-No, not at all)
   d. How do you feel about the present appearance of the scar?
      (Very satisfied-Satisfied-No opinion-Unsatisfied-Very unsatisfied)
2. Sensation in the abdomen
   a. Do you currently feel pain?
      (Continuously-Often-Occasionally-Not at all)
   b. Do you feel tightness in the scar?
      (Yes-No)
   c. Do you feel numbness around the scar?
      (Yes-A little-No)
   d. Do you have tactile and temperature sensation in the abdomen?
      (Yes-A little-No)
3. Activities of daily life
   a. Do you have any posture problems?
      (Yes-No)
   b. Is it difficult to look at yourself naked?
      (Yes-No)
   c. Did you experience any obstacles created by the scar when you returned to daily life?
      (Yes, several-A few-No, none)
   d. Do you have any referred pain?
      (Yes-No)
   e. How satisfied are you with your scar in daily life?
      (Very satisfied-Satisfied-No complaints-Unsatisfied-Very unsatisfied)

Space for free writing regarding impressions or complaints concerning the postoperative scars was also provided in the questionnaire. In addition, a schematic drawing of a body was attached to the questionnaire to allow for free drawing to express self-evaluated impressions (shape, length, site) and symptoms.

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Evaluation of immune function under conversion from Prograf to Advagraf in living donor liver transplantation

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Although some reports have shown the safety and efficacy of conversion from Prograf to Advagraf in liver transplantation, there have been no reports showing the change of immune function after conversion. The aim of this study is not only to analyze the safety and efficacy of conversion from Prograf to Advagraf, but also to evaluate the immune function using the ImmuKnow assay.

Material/Methods: Of the 168 living donor liver transplantation (LDLT) patients, 21 recipients whose liver function was stable after discharge in outpatient clinic and who agreed to conversion from Prograf to Advagraf were enrolled in this study. Liver, renal, and immune functions were retrospectively reviewed.

Results: There were no significant differences in liver and renal function after conversion from Prograf to Advagraf. The intracellular adenosine triphosphate levels before and after conversion were 263±157 and 256±133 ng/ml, respectively, and there was also no significant difference in immune function. None of the recipients showed adverse effects, rejection, or severe infection during the study. It should be further noted that none of the recipients had to increase the dose of Advagraf, while five of 21 recipients (24%) were able to reduce the dose of Advagraf during this study.

Conclusions: Conversion from Prograf to Advagraf in LDLT can be performed safely and effectively without affecting liver, renal, and immune function.

Key words: Advagraf • tacrolimus • ImmuKnow • LDLT

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Background

Immunosuppressive therapy is essential to preserve graft function in solid organ transplant recipients [1]. Prograf (Astellas Pharma, Inc.), which is a calcineurin inhibitor developed as an oral twice-daily medicine containing tacrolimus, has been the standard therapeutic regimen all over the world [2]. However, the oral twice-daily regimen has led to non-compliance, and non-compliance causes life-threatening rejection and late graft dysfunction [3,4]. To prevent this, Advagraf (Astellas Pharma, Inc.), a modified tacrolimus formation, was developed as an oral once-daily medicine. At present, conversion to Advagraf therapy has been accepted in various stable organ transplant recipients [5–11].

However, there have been no reports that show the actual changes of immune function after conversion. The ImmuKnow assay (Cylex™ ImmuKnow®-the Cylex Immune Cell Function Assay, Cylex, Inc., USA), which was approved by the Food and Drug Administration in 2002, has been shown to be capable of directly measuring the global immune response, especially T-cell-mediated immunity in transplant recipients. This assay has been shown to reliably distinguish between immune profiles of overimmunosuppression and underimmunosuppression and has been reported to be a convenient, non-invasive, *in vitro* assay, and to be effective as an immune monitoring tool for organ transplant recipients [12,13]. The aim of this study is to analyze the safety and efficacy of conversion from Prograf to Advagraf using not only liver and renal function but also immune function using the ImmuKnow assay.

Material and Methods

Patients

A total of 168 recipients underwent living donor liver transplantation (LDLT) from August 1997 to September 2011 at Nagasaki University Hospital. Of these recipients, 21 who underwent conversion from Prograf to Advagraf were enrolled in this study. They included 13 men and 8 women, with a median age at transplantation of 59 (range, 2–73). Original diagnoses included 3 hepatitis C virus (HCV) cirrhosis, 7 hepatitis B virus (HBV) cirrhosis, 5 alcoholic liver cirrhosis, and 6 others. Of these patients, 8 had hepatocellular carcinoma. The characteristics of the patients are shown in Table 1.

Table 1. The characteristic of the recipients.

Variable	Recipients (n=21)
Gender (male: female)	13: 8
Age	59 (2–73)
Original diagnosis*	HBV-LC: 2 HBV-LC/ HCC: 5 HCV-LC/ HCC: 3 Alcoholic LC: 5 BA: 4 FHF: 2
Duration between LDLT and conversion (months)	33 (7–171)
Duration after conversion (months)	8 (3–29)
Dose of Advagraf at conversion (mg/day)	2 (1–4)

* HBV – hepatitis B virus; HCV – hepatitis C virus; LC – liver cirrhosis; HCC – hepatocellular carcinoma; BA – biliary atresia; FHF – fulminant hepatic failure.

Protocol of immunosuppressant

The baseline protocol of immunosuppressants consisted of Prograf and steroids. The steroids were discontinued three to six months after staged reduction, as long as the liver function was stable without rejection. Prograf was initiated at the dose of 1 mg twice a day after transplantation, and regulated to adjust the desired tacrolimus trough level, 10–15 ng/ml within one month after transplantation and 5–10 ng/ml thereafter. In the outpatient clinic, Prograf was gradually reduced as long as the liver function was stable, and maintained at a minimal dose to prevent both adverse effects and rejection. The indications of the conversion were that liver functions had been stable for at least the three previous months in the outpatient clinic before conversion and that the recipient's fully informed consent to conversion was given. The initial dose after conversion to Advagraf started with the dose equivalent to the dose of Prograf at conversion.

Laboratory evaluation

Tacrolimus trough (Tac), total bilirubin (T-Bil), alanine aminotransferase (ALT), estimated Glomerular Filtration Rate (eGFR), serum creatinine (Cr), and fasting blood sugar (FBS) levels were recorded just before conversion and at the last follow-up and evaluated retrospectively.

The ImmuKnow assay

The immune function was evaluated using Cylex™ ImmuKnow®-the Cylex Immune Cell Function Assay (Cylex, Inc. USA). This assay

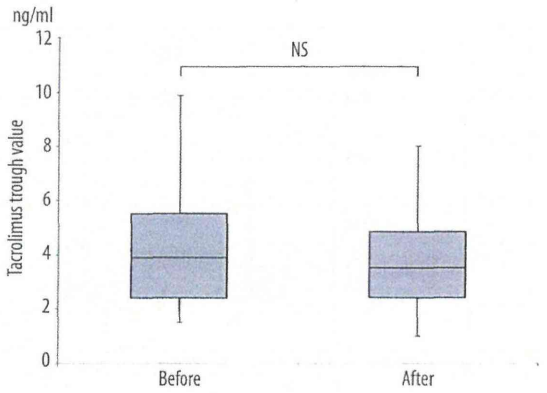

Figure 1. The change of the tacrolimus trough level before and after conversion. Tac levels before and after conversion were 3.9±2.4 and 3.5±2.1 ng/ml, respectively and there was no significant difference in Tac.

was performed according to the manufacturer's protocol [14]. A whole blood sample was collected from each recipient just before conversion and at the last follow-up. The blood sample was collected into an 8-ml sodium heparin vascutainer tube and tested within 10 hours. The whole blood was diluted with a sample diluent, added to a microtiter plate well, and incubated with phytohemagglutinin for 15 to 18 hours in a 37°C, 5% CO_2 incubator. The following day, CD4+ cells were positively selected within the microwells with magnetic particles coated with anti-human CD4 monoclonal antibody (Dynabeads, Dynal, Oslo, Norway) and a strong magnet (model 1050 magnet tray, Cylex, Inc., Columbia, MD) and washed to remove residual cells. A lysing reagent was added to release intracellular adenosine triphosphate (ATP). A luciferin/luciferase mixture was then added to the cell lysate. Within 10 minutes after the addition of the enzyme, released ATP was measured with a GloRunner™ Microplate Luminometer (Turner Biosystems CA).

Statistical analysis

Results for continuous variables were expressed as the median (range). Data for continuous variables were compared using the Mann-Whitney U test. We set statistical significance at $p<.05$.

Results

Change in Tac level and liver functions after conversion.

As shown in Figure 1, the Tac levels before and after conversion were 3.9±2.4 and 3.5±2.1 ng/ml, respectively, and there was no significant difference in Tac. Figure 2 shows liver function. The serum ALT levels before and after conversion were 25±13 and 25±19 IU/l, respectively, and the serum T-Bil levels were 0.9±0.5 and 30.9±0.5 mg/dl, respectively. There was no significant difference in liver function.

Change in renal functions and FBS levels after conversion

Figure 3 shows renal function and FBS level. The serum eGFR levels before and after conversion were 66.8±29.0 and 64.1±27.8 ml/min/1.73 m^2, the serum Cr levels were 0.87±0.23 and 0.82±0.27 mg/dl, and the serum FBS levels were 92±32 and 93±35 mg/dl, respectively. There was no significant difference in renal function or FBS level.

Change in ATP levels after conversion

Figure 4 shows the immune function. The ATP levels before and after conversion were 263±157 and 256±133 ng/ml, respectively. There was also no significant difference in immune function. In addition to these results, none of the recipients showed adverse effects, rejection, or severe

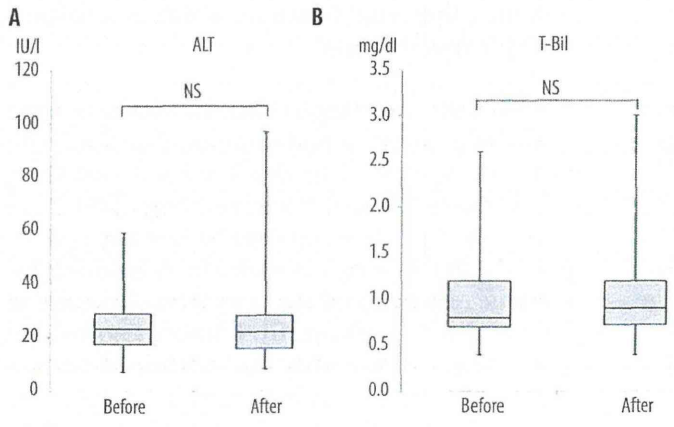

Figure 2. The change of liver functions before and after conversion. (**A**) Serum ALT levels before and after conversion were 25±13 and 25±19 IU/l, respectively. (**B**) Serum T-Bil levels were 0.9±0.5 and 30.9±0.5 mg/dl, respectively. There was no significant difference in liver function.

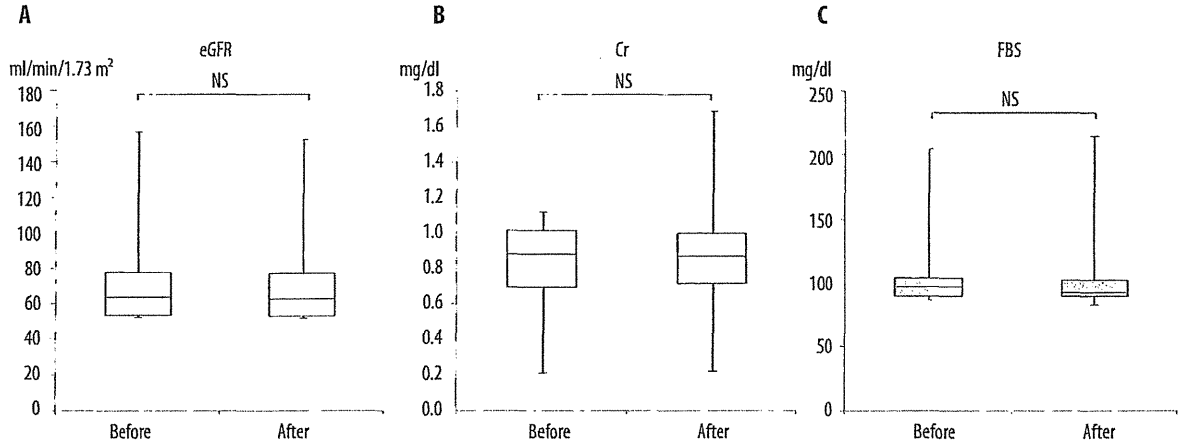

Figure 3. The change of renal functions and FBS before and after conversion. (**A**) Serum eGFR levels before and after conversion were 66.8±29.0 and 64.1±27.8 ml/min/1.73 m², respectively. (**B**) Serum Cr levels were 0.87±0.23 and 0.82±0.27 mg/dl, respectively. (**C**) Serum FBS levels were 92±32 and 93±35 mg/dl, respectively. There was no significant difference in renal functions or FBS level.

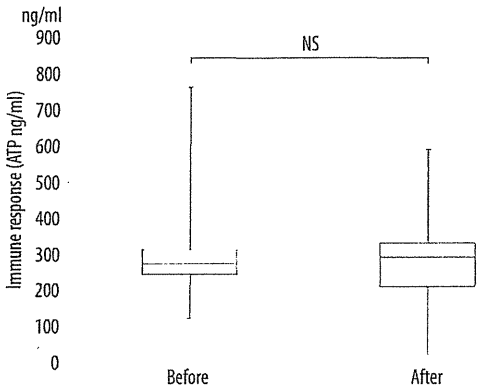

Figure 4. The change of immune function before and after conversion. ATP levels before and after conversion were 263±157 and 256±133 ng/ml, respectively. There was also no significant difference in immune function.

infection during the study. It should also be noted that none of the recipients had to increase the dose of Advagraf, and five of the recipients (24%) could reduce the dose of Advagraf without rejection during this study.

Discussion

Although some reports have shown the safety and efficacy of conversion from Prograf to Advagraf with regard to liver and renal function [8–11], the actual immune function has not yet been clarified. Liver transplantation has been the standard therapeutic option for end-stage liver diseases and reduces the mortality and morbidity of end-stage liver diseases as reflected in the 1- and 5-year survival rates [15–17]. This is mainly the result of improved immunosuppression due to the introduction of a calcineurin inhibitor. Prograf was the immediate-release form of tacrolimus and the oral twice-daily medicine used to prevent various complications in solid organ transplantations and has been accepted as the standard therapeutic regimen all over the world [2,18,19]. However, the estimated rates of nonadherence to immunosuppressive regimens in solid organ transplant recipients range from 15 to 55% [15–17]. Nonadherence has been identified as a leading cause of preventable graft loss [3,4]. It has been proposed that simpler dosing regimens, such as an oral once-daily regimen, may help to improve adherence in transplant recipients [20]. In fact, the prolonged-release form of tacrolimus (Advagraf) was developed as an oral once-daily medicine, and some data have shown that an oral once-daily regimen was associated with an increased likelihood of patient adherence compared with an oral twice-daily regimen [21]. Some reports have evaluated liver and renal function before and after conversion and have shown that the conversion can be applied to liver transplant recipients [8–11]. This study was also able to suggest that conversion does not affect liver and renal function, which is consistent with previous reports.

Additionally, we adapted the ImmuKnow assay to evaluate of the actual immune function. This assay was approved by the US Food and Drug Administration in 2002 for measuring CD4+ T cell immunity [5]. A meta-analysis by Kowaski et al. reported that this assay was useful in monitoring the immune response and assessing the relative risk of infection and rejection [6]. However, no reports have evaluated the safety and efficacy of conversion from Prograf to Advagraf with regard to immune function using this assay. As a result, there