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.

References

1. Marubashi S, Dono K, Nagano H, et al. Postoperative hyperbilirubinemia and graft outcome in living donor liver transplantation. *Liver Transpl.* 2007;13:1538–1544.
2. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology.* 1995;21:1317–1321.
3. Ikegami T, Nishizaki T, Yanaga K, et al. The impact of donor age on living donor transplantation. *Transplantation.* 2000;70:1703–1707.
4. Grande L, Rull A, Rimola A, et al. Outcome of patients undergoing orthotopic liver transplantation with elderly donors (over 60 years). *Transpl Proc.* 1997;29:3289–3290.
5. Japanese Liver Transplant Registry. Liver transplantation in Japan—registry by the Japanese Liver transplantation Society (in Japanese). *Isyoku.* 2010;45:621–632.
6. Wynne HA, Cope LH, Mutch E, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology.* 1989;9:297–301.
7. Wynne HA, Goudevenous J, Rawlins MD, et al. Hepatic drug clearance: the effect of age using indocyanine green as a model compound. *Br J Clin Pharmacol.* 1990;30:634–637.
8. Yoshizumi T, Taketomi A, Uchiyama H, et al. Graft size, donor age, and patient status are the indicators of early graft function after living donor liver transplantation. *Liver Transpl.* 2008;14: 1007–1013.
9. Rull R, Vidal O, Momblan D, et al. Evaluation of potential liver donors: limits imposed by donor variables in liver transplantation. *Liver Transpl.* 2003;9:389–393.
10. Cameron AM, Ghobrial RM, Hiatt JR, et al. Effect of nonviral factors on hepatitis C recurrence after liver transplantation. *Ann Surg.* 2006;244:563–571.
11. Ono Y, Kawachi S, Hayashida T, et al. The influence of donor age on liver regeneration and hepatic progenitor cell populations. *Surgery.* 2011;150:154–161.
12. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology.* 2008;47:143–152.
13. Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation.* 1999;67:321–327.
14. Felix D, Panco G, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant.* 2005;5:2605–2610.
15. Barri YM, Sanchez EQ, Jennings LW, et al. Acute kidney injury following liver transplantation: definition and outcome. *Liver Transpl.* 2009;15:475–483.

Surg Today (2013) 43:828–829
DOI 10.1007/s00595-013-0587-4

EDITORIAL

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

Susumu Eguchi

Received: 2 September 2012 / Accepted: 15 November 2012 / Published online: 17 April 2013

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].

This comment refers to the article available at doi:10.1007/s00595-012-0419-y.

S. Eguchi (✉)
Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
e-mail: sueguchi@nagasaki-u.ac.jp

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].

References

1. Hasegawa K, Takayama T, Orii R, Sano K, Sugawara Y, Imamura H, et al. Effect of hypoventilation on bleeding during hepatic resection: a randomized controlled trial. Arch Surg. 2002;137:311–5.
2. Zhu P, Lau WY, Chen YF, Zhang BX, Huang ZY, Zhang ZW, et al. Randomized clinical trial comparing infrahepatic inferior vena cava clamping with low central venous pressure in complex liver resections involving the Pringle manoeuvre. Br J Surg. 2012;99:781–8.
3. Rahbari NN, Koch M, Zimmermann JB, Elbers H, Bruckner T, Contin P, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. Ann Surg. 2011;253:1102–10.
4. Westerkamp AC, Lisman T, Porte RJ. How to minimize blood loss during liver surgery in patients with cirrhosis. HPB (Oxford). 2009;11:453–8.
5. Wang B, He HK, Cheng B, Sei K, Min S. Effect of low central venous pressure on postoperative pulmonary complications in patients undergoing liver transplantation. Surg Today. 2012. doi: 10.1007/s00595-012-0419-y (Epub ahead of print).
6. Pirat A, Ozgur S, Torgay A, Candan S, Zeyneloğlu P, Arslan G. Risk factors for postoperative respiratory complications in adult liver transplant recipients. Transplant Proc. 2004;36:218–20.
7. Feng ZY, Xu X, Zhu SM, Bein B, Zheng SS. Effects of low central venous pressure during preanhepatic phase on blood loss and liver and renal function in liver transplantation. World J Surg. 2010;34:1864–73.
8. Saner FH, Olde Damink SW, Pavlaković G, Sotiropoulos GC, Radtke A, Treckmann J, et al. How far can we go with positive end-expiratory pressure (PEEP) in liver transplant patients? J Clin Anesth. 2010;22:104–9.
9. Cywinski JB, Mascha E, You J, Argalious M, Kapural L, Christiansen E, Parker BM. Central venous pressure during the post-anhepatic phase is not associated with early postoperative outcomes following orthotopic liver transplantation. Minerva Anesthesiol. 2010;76:795–804.
10. Schroeder RA, Collins BH, Tuttle-Newhall E, Robertson K, Plotkin J, Johnson LB, Kuo PC. Intraoperative fluid management during orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 2004;18:438–41.
11. Eguchi S, Soyama A, Hidaka M, Takatsuki M, Muraoka I, Tomonaga T, Kanematsu T. Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus coinfection with special reference to hemophiliac recipients in Japan. Surg Today. 2011;41:1325–31.

Clin Transplant 2013: 27: E605–E610 DOI: 10.1111/ctr.12226

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.

Hajime Imamura, Akihiko Soyama, Mitsuhisa Takatsuki, Izumi Muraoka, Takanobu Hara, Izumi Yamaguchi, Takayuki Tanaka, Ayaka Kinoshita, Tamotsu Kuroki and Susumu Eguchi

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

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

Corresponding author: Susumu Eguchi, MD, PhD, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
Tel.: +81 95 819 7316; fax: +81 95 819 7319; e-mail: sueguchi@nagasaki-u.ac.jp

Conflict of interest: We do not disclose any commercial affiliations or consultancies of any of the authors that could be construed as a conflict of interest with respect to the submitted data. This work was not funded by any educational or commercial organization. No commercial organization was involved in the preparation of any part of this article.

Accepted for publication 29 July 2013

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

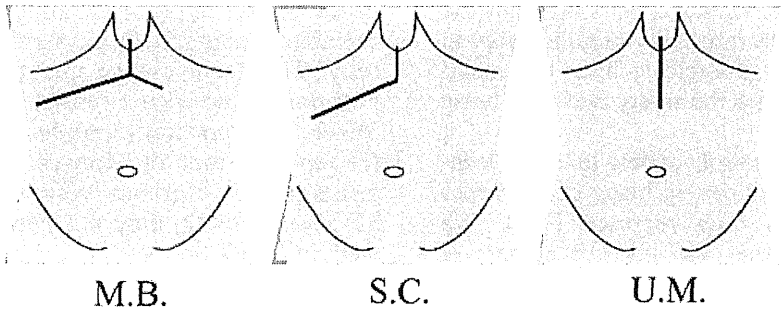

Fig. 1. The diagrams show the three types of incisions. From the left, M.B., Mercedes-Benz incision, S.C., right subcostal incision with midline up to xiphoid incision, U.M., short upper midline incision.

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.

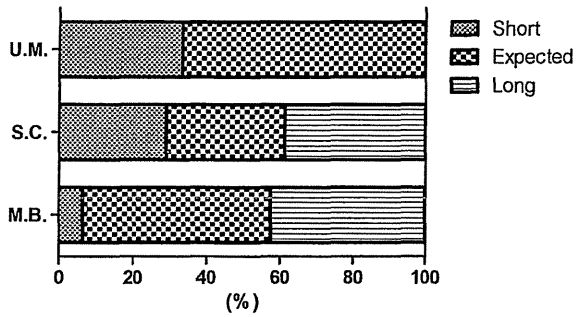

Fig. 2. The details of 1.a. (How do you feel about the length of your postoperative scar compared with the image you had before surgery?). The shorter the total length of incisions became the rate of "shorter" or "as expected" increased. In the upper midline incision group, the donors tended to consider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

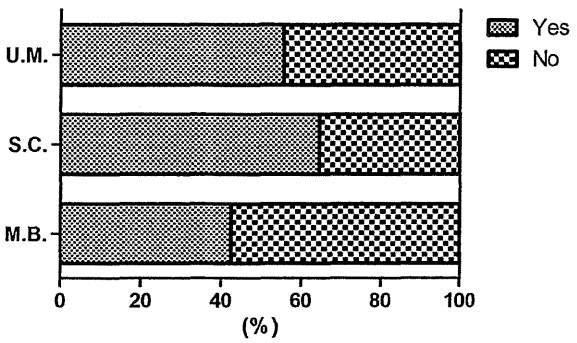

Fig. 3. The details of 2.a. (Do you currently feel pain?). In all groups, some of the donors reported current continuous pain. The area of pain was present around their scar. In the Mercedes-Benz incision group, 42% of the donors reported continuous pain even 168 months after the operation.

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

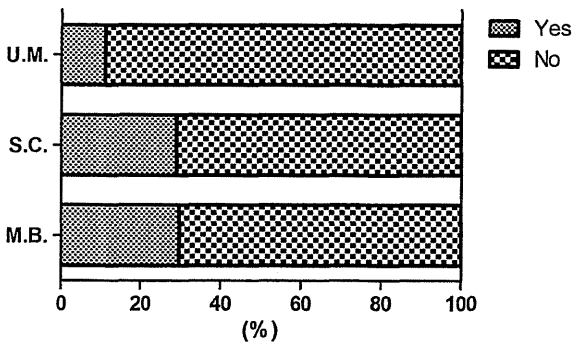

Fig. 4. The details of 2.c. (Do you feel numbness around the scar?). The rate of numbness was 30% (n = 14) in the Mercedes-Benz incision group and 29% (n = 9) in the right subcostal incision with midline up to xiphoid incision group, whereas only one donor in the short upper midline incision group (11%)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

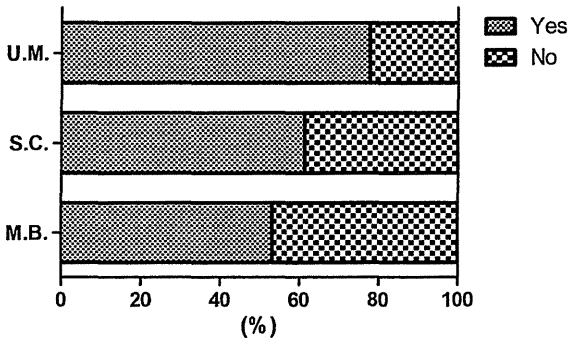

Fig. 5. The details of 2.d. (Do you have tactile and temperature sensation in the abdomen?). A loss of cutaneous sensation was observed in 47% of the donors in the Mercedes-Benz incision group (n = 22), 39% of the donors in the right subcostal incision with midline up to xiphoid incision group (n = 12),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

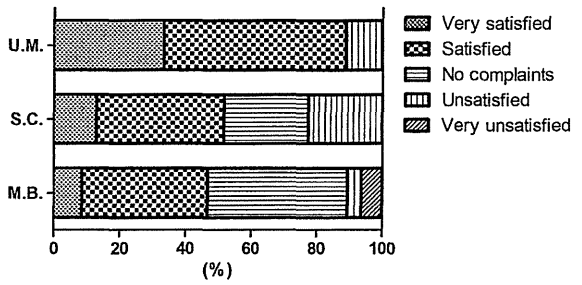

Fig. 6. The details of 3.e. (How satisfied are you with your scar in daily life?). Current evaluation of the scars in daily life. Eighty-nine percent of the donors in the short upper midline incision group were currently satisfied with their scars.

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.

References

1. Koffron AJ, Kung R, Baker T, Fryer J, Clark L, Abecassis M. Laparoscopic-assisted right lobe donor hepatectomy. Am J Transplant 2006: 6: 2522.
2. Nitta H, Sasaki A, Fujita T et al. Laparoscopy-assisted major liver resections employing a hanging technique: the original procedure. Ann Surg 2010: 251: 450.
3. Soubrane O, Cherqui D, Scatton O et al. Laparoscopic left lateral sectionectomy in living donors: safety and reproducibility of the technique in a single center. Ann Surg 2006: 244: 815.
4. Soyama A, Takatsuki M, Hidaka M et al. Standardized less invasive living donor hemihepatectomy using the hybrid method through a short upper midline incision. Transplant Proc 2012: 44: 353.
5. DuBay DA, Holtzman S, Adcock L et al. Cosmesis and body image after adult right lobe living liver donation. Transplantation 2010: 89: 1270.
6. Togashi J, Sugawara Y, Tamura S et al. Donor quality of life after living donor liver transplantation: a prospective study. J Hepatobiliary Pancreat Sci 2011: 18: 263.
7. Parikh ND, Ladner D, Abecassis M, Butt Z. Quality of life for donors after living donor liver transplantation: a review of the literature. Liver Transpl 2010: 16: 1352.

8. Dunker MS, Stiggelbout AM, van Hogezand RA, Ringers J, Griffioen G, Bemelman WA. Cosmesis and body image after laparoscopic-assisted and open ileocolic resection for Crohn's disease. Surg Endosc 1998: 12: 1334.
9. Lind MY, Hop WC, Weimar W, IJzermans JN. Body image after laparoscopic or open donor nephrectomy. Surg Endosc 2004: 18: 1276.
10. Sucullu I, Filiz AI, Canda AE, Yucel E, Kurt Y, Yildiz M. Body image and cosmesis after laparoscopic or open appendectomy. Surg Laparosc Endosc Percutan Tech 2009: 19: 401.
11. Jain A, Nemitz P, Sharma R et al. Incidence of abdominal wall numbness post-liver transplantation and its complications. Liver Transpl 2009: 15: 1488.
12. Chan SC, Liu CL, Lo CM et al. Donor quality of life before and after adult-to-adult right liver live donor liver transplantation. Liver Transpl 2006: 12: 1529.
13. Verbesey JE, Simpson MA, Pomposelli JJ et al. Living donor adult liver transplantation: a longitudinal study of the donor's quality of life. Am J Transplant 2005: 5: 2770.

© Ann Transplant, 2013: 18: 293-298
DOI: 10.12659/AOT.883953

WWW.annalsoftransplantation.COM
Original Paper

Received: 2012.12.12
Accepted: 2013.04.08
Published: 2013.06.14

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

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

Takayuki Tanaka[ABCDEF], Mitsuhisa Takatsuki[ABCDEF], Akihiko Soyama[AD], Yasuhiro Torashima[B], Ayaka Kinoshita[B], Izumi Yamaguchi[B], Tomohiko Adachi[C], Amane Kitasato[C], Tamotsu Kuroki[D], Susumu Eguchi[AEF]

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

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

Full-text PDF: http://www.annalsoftransplantation.com/download/index/idArt/883953

Word count: 1455
Tables: 1
Figures: 4
References: 21

Author's address: Susumu Eguchi, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan, zip code,852-8501, e-mail: sueguchi@nagasaki-u.ac.jp

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

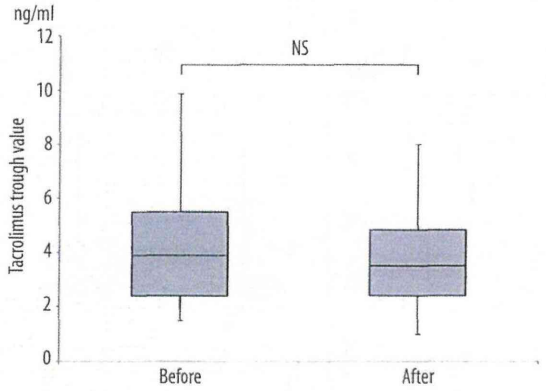

Figure 1. The change of the tacrolimus trough level before and after conversion. Tac levels before and after conversion were 3.9±2.4 and 3.5±2.1 ng/ml, respectively and there was no significant difference in Tac.

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

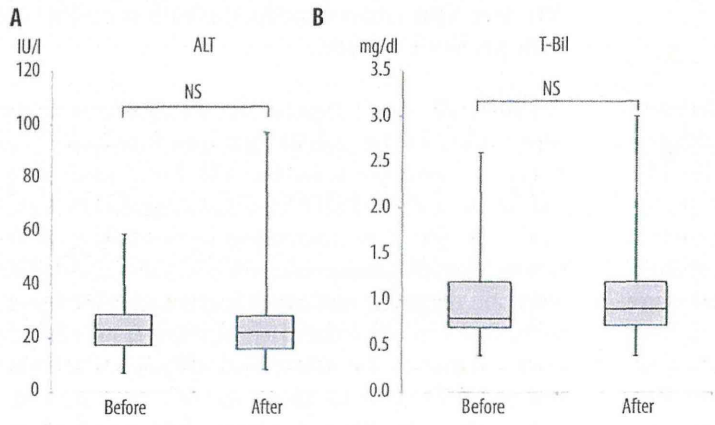

Figure 2. The change of liver functions before and after conversion. **(A)** Serum ALT levels before and after conversion were 25±13 and 25±19 IU/l, respectively. **(B)** Serum T-Bil levels were 0.9±0.5 and 30.9±0.5 mg/dl, respectively. There was no significant difference in liver function.

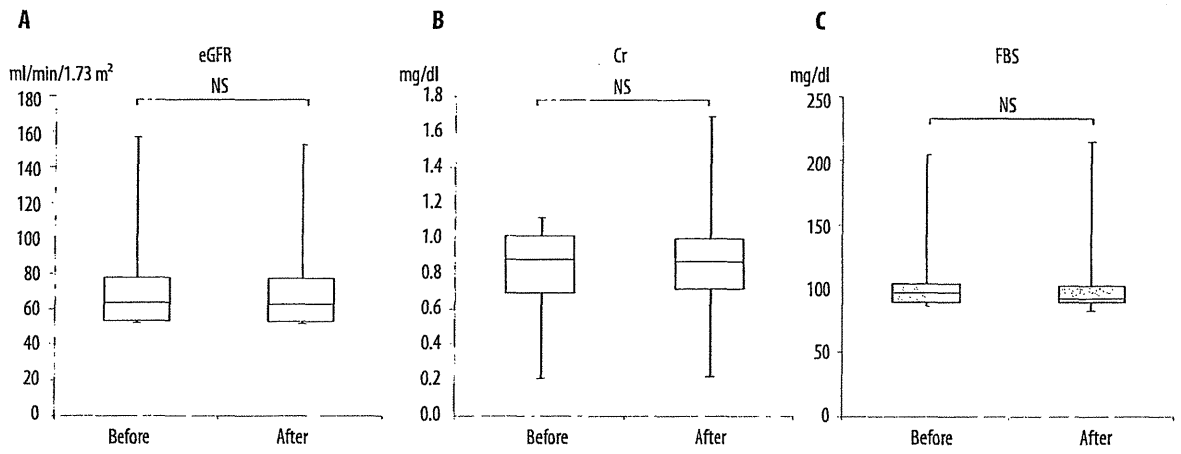

Figure 3. The change of renal functions and FBS before and after conversion. (**A**) Serum eGFR levels before and after conversion were 66.8±29.0 and 64.1±27.8 ml/min/1.73 m², respectively. (**B**) Serum Cr levels were 0.87±0.23 and 0.82±0.27 mg/dl, respectively. (**C**) Serum FBS levels were 92±32 and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

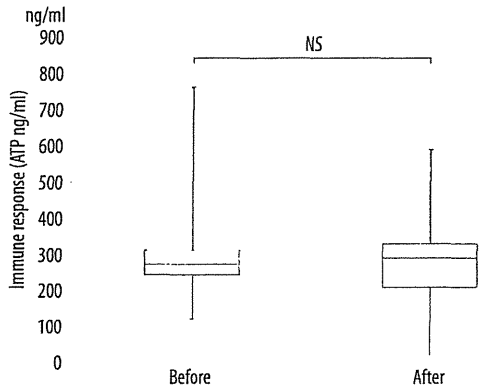

Figure 4. The change of immune function before and after conversion. ATP levels before and after conversion were 263±157 and 256±133 ng/ml, respectively. There was also no significant difference in immune function.

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

was no significant difference in immune function before and after conversion; this result suggested that conversion also did not affect immune function. In addition, it was important that none of the recipients showed adverse effects, rejection, or severe infection and none had to increase the dose of Advagraf, while five of 21 recipients (24%) were even able to reduce the dose of Advagraf during this study. In our policy of immunosuppression, especially in long-term cases, we reduce and maintain the dose of immunosuppressant as long as possible, keeping the lowest level of tacrolimus needed to prevent rejection. According to the results of this study, Advagraf might be a feasible treatment for avoiding an overdose of tacrolimus.

Conclusions

This study suggested that the conversion of Advagraf can be safely and effectively applied to stable LDLT recipients without affecting liver, renal, and immune function.

Disclosure

The authors have no conflicts of interest or funding to disclose.

References:

1. Chapman JR: The KDIGO clinical practice guideline for the care of kidney transplant recipients. Transplantation, 2010; 89: 644–45
2. Weiler N, Thrun I, Hoppe-Lotichius M et al: Early steroid-free immunosuppression with FK506 after liver transplantation: long-term results of a prospectively randomized double-blinded trial. Transplantation, 2010; 90: 1562–66
3. Gaston RS, Hudson SL, Ward M et al: Late renal allograft loss: noncompliance masquerading as chronic rejection. Transplant Proc, 1999; 31: 21S–23S
4. Denhaerynck K, Dobbles F, Cleemput I et al: Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int, 2005; 18: 1121–33
5. van Hooff JP, Alloway RR, Trunečka P, Mourad M: Four-year experience with tacrolimus once-daily prolonged release in patients from phase II conversion and *de novo* kidney, liver, and heart studies. Clin Transplant, 2010; 25: E1–12
6. Iaria G, Sforza D, Angelico R et al: Switch from twice-daily tacrolimus (Prograf) to once-daily prolonged-release tacrolimus (Advagraf) in kidney transplantation. Transplant Proc, 2011; 43: 1028–29
7. Calia R, Lai C, Aceto P et al: Effects of switching from twice-daily to once-daily tacrolimus formulation on quality of life, anxiety, and transplant benefit perception after kidney transplantation. Transplant Proc, 2011; 43: 1020–23
8. Marin-Gomez LM, Gomez-Bravo MA, Alamo-Martinez JA et al: Evaluation of clinical safety of conversion to Advagraf therapy in liver transplant recipients: observational study. Transplant Proc, 2009; 41: 2184–86
9. Trunečka P, Boillot O, Seehofer D et al: Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-dailiy tacrolimus (PROGRAF) in liver transplantation. Am J Transplant, 2010; 10: 2313–23
10. Comuzzi C, Lorenzin D, Rossetto A et al: Safety of conversion from twice-daily tacrolimus (Prograf) to once-daily prolonged-release tacrolimus (Advagraf) in stable liver transplant recipients. Transplant Proc, 2010; 42: 1320–21
11. Perrakis A, Schwarz K, Yedibela S et al: Impact of the conversion of the immunosuppressive regimen from Prograf to Advagraf or to Sirolimus in long-term stable liver transplant recipients: indication, safety, and outcome. Transplant Proc, 2011; 43: 3702–7
12. Kowalski RJ, Post DR, Schneider MC et al: Immune cell function testing: an adjunct to therapeutic drug monitoring in transplant patient management. Clin Transplant, 2003; 17: 77–88
13. Kowalski RJ, Post DR, Mannon RB et al: Assessing relative risks of infection and rejection: a meta-analysis using an immune function assay. Transplantation. 2006; 82: 663–68
14. Sottong PR, Rosebrock JA, Britz JA, Kramer TR: Measurement of T-lymphocyte responses in whole-blood cultures using newly synthesized DNA and ATP. Clin Diagh Lab Immunol, 2000; 7: 307–11
15. O'Carroll RE, McGregor LM, Swanson V et al: Adherence to medication after liver transplantation in Scotland: a pilot study. Liver Transplant, 2006; 12: 1862–68
16. Butler JA, Roderick P, Mullee M et al: Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation, 2004; 77: 769–76
17. Vasquez EM, Tanzi M, Benedetti E, Pollak R: Medication noncompliance after kidney transplantation. Am J Health Syst Pharm, 2003; 60: 266–69
18. Kelly PA, Burckart GJ, Venkataramanan R: Tacrolimus: a new immunosuppressive agent. Am J Health Syst Pharm, 1995; 52: 1521–35
19. Spencer CM, Goa KL, Gillis JC: Tacrolimus. An update of its pharmacology and clinical efficacy in the management of organ transplantation. Drugs, 1997; 54: 925–75

20. Morrissey PE, Flynn ML, Lin S: Medication noncompliance and its implications in transplant recipients. Drugs, 2007; 67: 1463–81

21. Weng FL, Israni AK, Joffe MM et al: Race and electronically measured adherence to immunosuppressive medications after decreased donor renal transplantation. J Am Soc Nephrol, 2005; 6: 1839–48

ELSEVIER

Clinical Outcome of Pancreas Transplantation From Marginal Donors in Japan

Y. Tomimaru, T. Ito, K. Kawamoto, N. Hama, H. Wada, S. Kobayashi, H. Eguchi, M. Tanemura, M. Mori, Y. Doki, and H. Nagano

ABSTRACT

In Japan, absolute shortage of donors still continues even after the law allowing organ transplantation from deceased donors came into force in 1997. With the passage of the waiting period after registration for pancreas transplantation (PTx), both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Therefore, so-called "marginal donor" (MD) has been considered as a potential solution for shortage of donors in Japan. The aim of the present study is to evaluate feasibility of MD in terms of post-PTx outcomes using data from Japan Organ Transplantation Network. A total of 148 PTx were performed from deceased donors in Japan from 2000 to 2012. MD was defined as follows: (1) >45 years old; (2) hemodynamically unstable at harvest using a high-dose dopamine or more than 2 vasopressors; or (3) non–heart-beating status. Postoperative outcomes after PTx were compared between the MD group and the non-MD group. Among the 148 PTx donors, 108 donors (73.0%) satisfied the criteria of MD. Early graft loss of pancreas graft during 3 months post-transplant was observed in 15 patients (10.1%), and the marginality (MD vs non-MD) was not significantly correlated with the early loss of pancreas graft. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from that of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%). Pancreas graft survival in the MD group (1, 3, 5 years: 80.9%, 73.2%, 66.0%) seemed to be slightly lower than that in the non-MD group (1, 3, 5 years: 92.5%, 85.2%, 77.4%), but no statistically significant differences were found between the 2 groups. These results suggest the feasibility of the use of MD for PTx.

PANCREAS TRANSPLANTATION (PTx) is an established treatment for type 1 diabetes [1–3]. It is the only effective therapeutic option to restore normal glucose metabolism, to improve quality of life of the patients, and to even reduce chronic complications of the diabetes. Although its outcome was not satisfactory previously, graft survival has much improved during the last 30 years because of development in immunosuppressants, surgical techniques, and postoperative management.

In Japan, the Organ Transplant Law was enforced on October 1997, and it was revised on July 2010. Since the revision, the number of donation is increasing. However, absolute shortage of donors still continues even after the revision. With the passage of the waiting period after registration for PTx, both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Accordingly, we have had to depend on the so-called "marginal donor" (MD). To date, however, the feasibility of PTx from MD has not yet investigated well. In this regard, the present study was performed to evaluate its feasibility in terms of postoperative outcomes using data from Japan Organ Transplantation Network.

From the Departments of Surgery (Y.T., T.I., K.K., N.H., H.W., S.K., H.E., M.T., M.M., Y.D., H.N.) and Complementary & Alternative Medicine (T.I.), Osaka University, Graduate School of Medicine, Osaka, Japan; The Japan Registry of Pancreas Transplantation (T.I.), Japan; and The Japan Society for Pancreas and Islet Transplantation (T.I.), Suita, Osaka, Japan.

Address reprint requests to Hiroaki Nagano, MD, PhD, and Toshinori Ito, MD, PhD, Department of Surgery, Osaka University, Graduate School of Medicine, 2-2 Yamadaoka, Suita, 565-0871 Osaka, Japan. E-mail: hnagano@gesurg.med.osaka-u.ac.jp or juki@cam.med.osaka-u.ac.jp

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.11.069

PATIENTS AND METHODS

Patients

Between April 2000 and December 2012, a total of 148 PTx were performed for type 1 diabetes from deceased donors in Japan. Among the 148 cases of PTx, 146 cases were from brain-dead donors and the remaining 2 were non–heart-beating donors. In Japan, PTx is performed in 17 approved institutions. Characteristics of the 148 patients are shown in Table 1.

Criteria of Marginal Donor

The criteria of MD for PTx of Kapur et al were used in this study; donors of 45 years of age and more, hemodynamically unstable donors at the time of harvest (with dopamine dose > 10 μg/k/min, or 2 or more vasopressors), or non–heart-beating donors [4]. Based on these criteria, the donors were divided into 2 groups: the MD group and the non-MD group.

Graft Failure

Pancreas graft failure was defined as return to insulin-dependence or serum C-peptide level < 0.3 ng/mL. Kidney graft failure was defined as return to dialysis. Death with a functioning graft was also considered be a graft failure. Early graft loss was defined as that within 3 months post-PTx in this study.

Statistical Analysis

Survival was calculated according to the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC, United States). A P value <.05 was considered statistically significant.

Table 1. Characteristics of 148 PTx Patients (n = 148)

Factors	
Donor-related factors	
Age (≤45 y/>45 y)	74/74
Gender (male/female)	80/68
Body mass index (kg/m^2) (<25/≥25)	115/33
Cause of death (CVA/trauma/others)	87/28/33
Type of death (brain-dead/non–heart-beating)	146/2
Hemodynamics (stable/unstable)	87/61
Cardiopulmonary resuscitation (−/+)	86/62
Marginality (MD/non-MD)	108/40
Recipient-related factors	
Age (≤50 y/>50 y)	123/25
Gender (male/female)	56/92
Duration of diabetes (<30 y/≥30 y)	90/58
Duration of dialysis (<10 y/≥10 y)	72/47
PTx-related factors	
TCIT (<12 h/≥12 h)	86/62
Type of PTx (SPK/PAK/PTA)	119/20/9
Duct management (bladder drainage/enteric drainage)	30/118
GDA reconstruction (−/+)	35/87
Immunosuppressive regimen	
CNI (TAC/CyA)	144/4
Antibody (−/+)	7/141

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time; SPK, simultaneous pancreas and kidney transplantation; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; GDA, gastroduodenal artery; CNI, calcineurin inhibitor; TAC, tacrolimus; CyA, cyclosporine.

RESULTS

Ratio of Marginal Donors

Among the 148 donors at the PTx, 74 were 45 or more years old. Sixty-one donors were hemodynamically unstable at the time of harvest. Two donors were non–heart-beating donors. In total, 108 donors (73.0%) of the 148 donors satisfied the criteria of MD and categorized into the MD group, and the remaining 40 donors (27.0%) were categorized into the non-MD group. Characteristics of the 148 patients are shown in Table 1.

Risk Factors for Early Loss of Pancreas Graft

Among the 148 PTx cases, early graft loss of pancreas graft was observed in 15 patients (10.1%). Thrombosis was the most frequent cause of the graft loss (8/15, 53%). The other causes were as follows: sepsis in 3, rejection in 2, duodenal perforation in 1, and cardiogenic shock in 1.

To investigate whether the marginality (MD vs non-MD) is a risk factor for the early loss of pancreas graft, as well as to identify factors that significantly correlate with the early graft loss, donor-related factors were compared between cases with the early graft loss and without the early graft loss (Table 2). The incidence of the early graft loss was significantly higher in donors with total cold ischemic time (TCIT) ≥12 hours (P = .05), and the marginality (MD vs non-MD) was not significantly correlated with the graft loss.

Long-Term Outcome After Pancreas Transplantation

We examined long-term outcomes of PTx in terms of overall patient survival, pancreas graft survival, and kidney graft survival (SPK cases). As shown in Table 3, in all the 148 cases, postoperative mortality was found in 5 patients in the MD group (4.6%) and in 3 patients in the non-MD group (7.5%). The incidence was not significantly different between the 2 groups (P = .45). Overall patient survival in the 148 cases was 94.8%, 94.8%, and 94.8% at 1, 3, and 5 years, respectively. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from those of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%; P = .42, Fig 1A). Twenty-four pancreas grafts were lost during the observation period

Table 2. Correlation of Donor-Related Factors With Early Loss of Pancreas Graft in the 148 PTx Cases

Factor	Early Graft Loss (−) (n = 133)	Early Graft Loss (+) (n = 15)	P Value
Age (≤45 y/<45 y)	66/67	8/7	.79
Gender (male/female)	70/63	10/5	.41
Body mass index (kg/m^2) (<25/≥25)	103/30	12/3	.56
Cause of death (CVA/others)	78/55	10/5	.59
Hemodynamics (stable/unstable)	80/53	7/8	.41
Cardiopulmonary resuscitation (−/+)	78/55	8/7	.78
TCIT (<12 h/≥12 h)	81/52	5/10	.05
Marginality (MD/non-MD)	96/37	12/3	.76

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time.

Table 3. Incidence of Mortality and Graft Failures in MD Group and Non-MD Group

	MD Group	Non-MD Group	*P* Value
Mortality	5/108 (4.6%)	3/40 (7.5%)	.45
Cardiogenic	1	2	
Cerebral bleeding	1	0	
Sepsis	2	1	
GVHD	1	0	
Pancreas graft failure	24/108 (22.2%)	4/40 (10.0%)	.08
Thrombosis	7	1	
Duodenal perforation/ bleeding	2	0	
Pancreatitis	1	0	
Recurrent diabetes	2	0	
Rejection	12	3	
Kidney graft failure	8/88 (9.1%)	1/31 (3.2%)	.44
Thrombosis	0	0	
Primary nonfunction	1	0	
Rejection	7	1	

Abbreviations: MD, marginal donor; GVHD, graft-versus-host disease.

among the 108 cases in the MD group, and 4 pancreas grafts were lost in the 40 cases in the non-MD group (Table 3). The incidence of the pancreas graft failure in the MD group tended to be higher than the non-MD group ($P = .08$, Table 3). Especially, thrombosis and rejection were frequently observed as a cause of the graft failure in the MD group. Pancreas graft survival in all the 148 cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Pancreas graft survival in the MD group and the non-MD group was 80.9% and 92.5%, 73.2% and 85.2%, and 66.0% and 77.4% at 1, 3, and 5 years post-PTx, respectively, and there was no significant difference between the 2 groups ($P = .35$, Fig 1B). Incidence of kidney graft failure in 119 SPK cases was also compared. The incidence was not significantly different between the 2 groups ($P = .44$, Table 3). Kidney graft survival in the SPK cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Kidney graft survival of the MD group (1, 3, 5 years: 89.1%, 89.1%, 86.0%) was not significantly different from that of the non-MD group (1, 3, 5 years: 93.5%, 93.5%, 84.2%; $P = .77$, Fig 1C).

DISCUSSION

The present study first showed that MD has been mostly utilized for PTx in Japan, compared with the condition of PTx donors in the United States [2,3]. However, the patient survival and graft survival were not significantly different from that in the United States. In case of simultaneous liver harvest in Japan, the reconstruction of gastroduodenal artery in pancreas graft has been done as much as possible (71.3%) to increase the blood flow in pancreas head region [5]. It remains unknown whether this procedure will have an effect on the early graft outcome.

The present study also demonstrated that there are no statistically significant differences in long-term outcomes after PTx between the MD group and the non-MD group. Furthermore, we investigated risk factors for the early loss of pancreatic graft and found that the marginality (MD vs non-MD) is not statistically significantly correlated with the early loss. These findings suggested the possibility that PTx from MDs is feasible in terms of postoperative outcomes. We also showed that the incidence of the early pancreatic graft loss within 3 months posttransplant is significantly increased when TCIT is over 12 hours. On the other hand, in the United States, it has been reported that preservation time of pancreatic graft >20 hours is significantly associated with post-PTx complications [6,7]. In this regard, a permissive range of the preservation time is likely to be narrow in Japan as compared to the United States where non-MDs are mostly available.

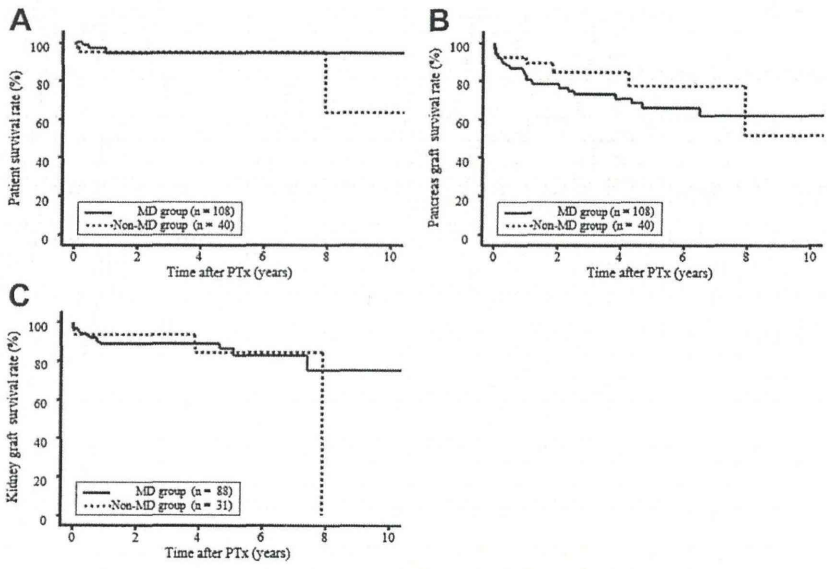

Fig 1. Long-term outcome after pancreas transplantation. Overall patient survival (**A**), pancreas graft survival (**B**), and kidney graft survival (**C**) were compared between the MD group (solid lines) and the non-MD group (dotted lines). Overall patient survival and pancreas graft survival were calculated in all the 148 PTx cases, and kidney graft survival was calculated in 119 simultaneous pancreas and kidney transplantation cases. Survival was not significantly different between the 2 groups. MD, marginal donor; PTx, pancreas transplantation.