指腸穿孔により摘出された。他に，1例が急性拒絶（POD；45日）で摘出，8例が慢性拒絶反応などの理由で，それぞれ移植後4カ月～4年7カ月でインスリン再導入となった。さらに，前記死亡例を含めると，計23例が移植膵の機能喪失となった。1年，3年，5年生着率はそれぞれ85.7%，79.4%，72.1%であった（**図15**）。

一方，SPK症例の移植腎の生着については，101症例中，1例がPNF（primary non-function），1例は急性拒絶（POD；51日）で摘出，他に6例がそれぞれ，10カ月から7年5カ月で透析再導入となった。前記死亡例を含めると，計13例が機能喪失となった。その結果，1年，3年，5年腎生着率はそれぞれ91.3%，91.3%，85.3%であった。

4. 生体膵臓移植について

生体ドナーから行われた膵臓移植症例25例における上記関連因子について解析した。

ドナーは20例が両親のどちらか（母；13例，父；7例）からであり，3例が兄弟から，2例が姉妹から提供された。多くは父母からの提供であるため，ドナーの平均年齢は56.6(28～72)歳と高齢であった。一方，レシピエントは男性10例，女性15例で，平均年齢は36.0（25～50）歳であった。カテゴリー別では，SPKが21例と最も多く，ついでPTAの3例，PAKが1例であった。術式別では，脳死・心停止下とは異なり，大半がBD（20例）でありEDは5例であった。免疫抑制療法は脳死・心停止下の場合と同様であった。

移植成績：1例が移植1年後，脳梗塞にて死亡した。これはPAKの1例で，移植膵は機能するも，膵移植後2カ月で移植腎の機能が増悪して透析再導入となった症例であった。SPKの4例で急性期に機能が喪失した。1例はPNFで，3例は血栓症にて移植膵を摘出しインスリン再導入となった。また，慢性期に3例がインスリン再導入となった。なお，PAKやPTAの場合には，膵臓移植前に移植腎の機能を慎重に評価しなければならない。

IV. まとめと今後の展望

以上，2011年末までの膵臓移植症例146例について，その解析結果を報告した。本邦ではmarginal caseが多く，ドナーの条件は良くはないが，移植成績は欧米のそれと比較して，決して遜色のない結果である。なお，2010年7月17日の臓器移植法改正後，2011年12月末までに73例の臓器提供（うち，膵の提供は57例）があり，このうち，多くが家族の承諾であった。今後はさらに，臓器提供の増加が見込まれ，それに向けたスムーズな対応とその体制が必要となる。

文責：膵・膵島移植研究会
膵臓移植症例登録委員会事務局
伊藤壽記

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特集「法改正後の移植の現状と問題点：腎膵領域」

法改正後の膵臓移植の現状

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はじめに

本邦において，「臓器の移植に関する法律」，いわゆる“臓器移植法”が1997年10月16日に実施されたが，この法律は実施に至る条件が厳格に制限されており，世界の標準からは随分かけ離れたものであった。したがって，その後の脳死下での臓器提供は年間平均10例弱に過ぎず，臓器移植治療しかない患者にとってそのニーズに応えるにはほど遠い法律であった。そのため，膵臓移植レシピエントにおいても，登録後の待機期間が延び，その間に糖尿病合併症で死亡したり，状態が悪化して登録を取り下げざるを得ない患者が増える事態が生じてきた。同法は当初3年後の見直しを条件とした暫定法であったが，各部署からの要請にもかかわらず，3年経っても見直しされることがなかった。そして，くしくも臓器移植法施行後初の脳死下での膵臓移植10年目に当たる2010年（7月17日）に，改正臓器移植法が実施される運びとなった。

本稿では，法改正の前後で膵臓移植の状況がどう影響を受けたかについて述べてみたい。

本邦における死体臓器提供の年次推移

臓器移植法実施からの臓器移植提供数の年次推移が示されている（**図1**）。臓器移植法改正前では，脳死下での臓器提供は12年9カ月でわずかに86例しかみられなかったが，改正後は予想に反して，2011年12月末までの1年6カ月で73例と約7.4倍の急速な増加がみられた。そのうち，膵臓移植でみてみると，改正前は64例であったが，改正後は2011年12月末までで57例であった。増加率は約7.8倍とほぼ同様であった。そして，こうした臓器提供の多くが本人の意思表示によるものではなく，ご遺族の同意のみで行われたことを考えると，今回の臓器移植法改正の意義がうかがわれる。

なお，心停止下での腎提供（献腎）については，法改正までは，年平均84例であったが，改正時の2010年は81例，さらに2011年は68例とやや減少している傾向がうかがえる（**図2**）。これは，献腎の提供施設の約半数が脳死判定可能な，いわゆる4類型の医療施設である関係で，これまでの心停止下での臓器提供が脳死下での提供に移行していると考えられる。

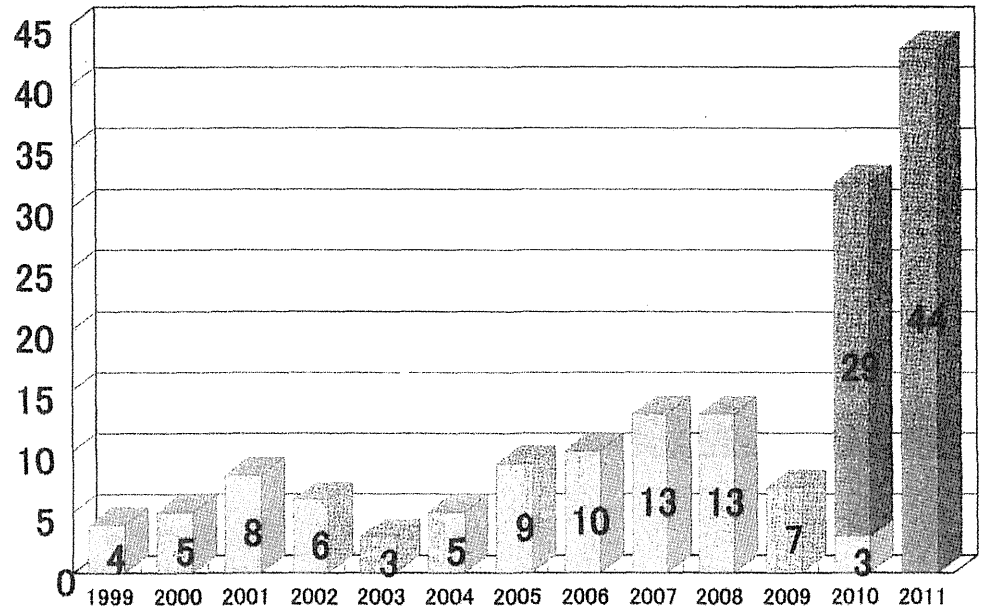
また，1ドナー当たりの平均移植患者数ならびに平均移植臓器数をみてみると，確かに法改正後はともにやや低下した感は否めない（**図3**）。しかしながら，本邦での1ドナー当たりの平均移植臓器数をみると5を越えており，米国の3.05をはるかに凌駕している。

法改正前・後の膵臓移植について

1. 待機レシピエントについて

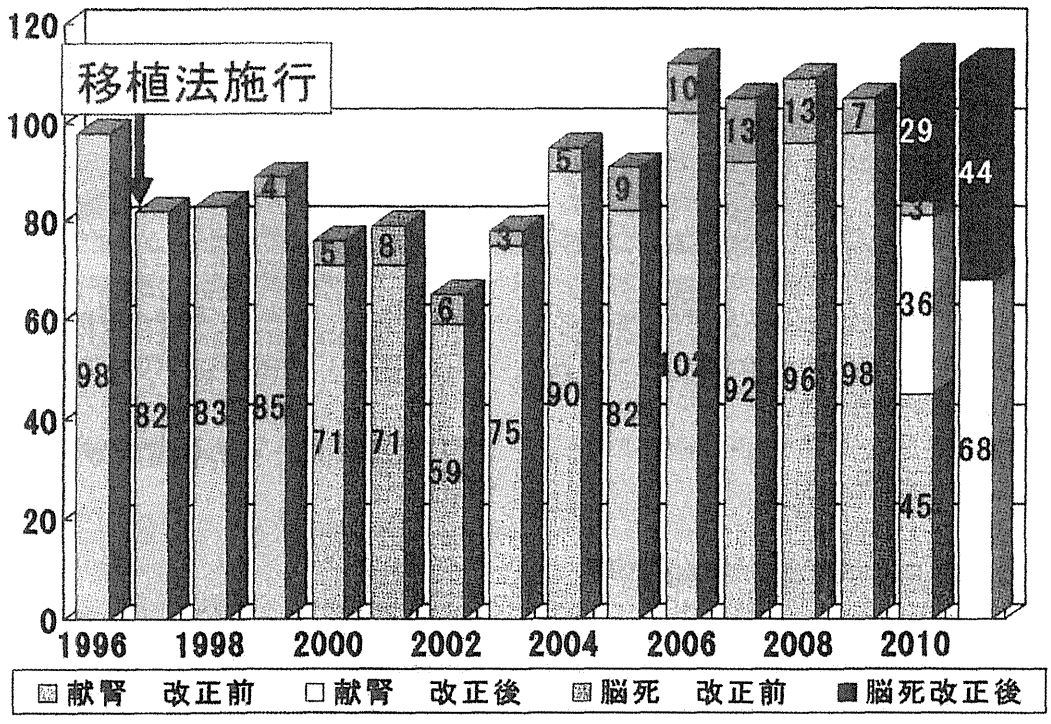
膵臓移植のレシピエント登録は，1999年10月から開始され，年間25名前後が新規に登録されていたが，改正後のほぼ2年間で68名と増加がみられた。2011年12月末で計198名が待機中である。性別では女性が133名と男性の65名の約2倍であり，年齢別では40歳代が87名と最も多く，次いで50歳代（55名），30歳代（40名）と続く（**図4**）。問題は待機期間であり，5年以上の待機者は，2010年末の調査では67名（38%）であったが，2011年末では60名（30%）と，

図1　わが国の脳死臓器提供の推移



(～2011. 12. 31)

図2　わが国の献腎数の推移



(～2011. 12. 31)

図３　わが国の脳死臓器提供数の推移

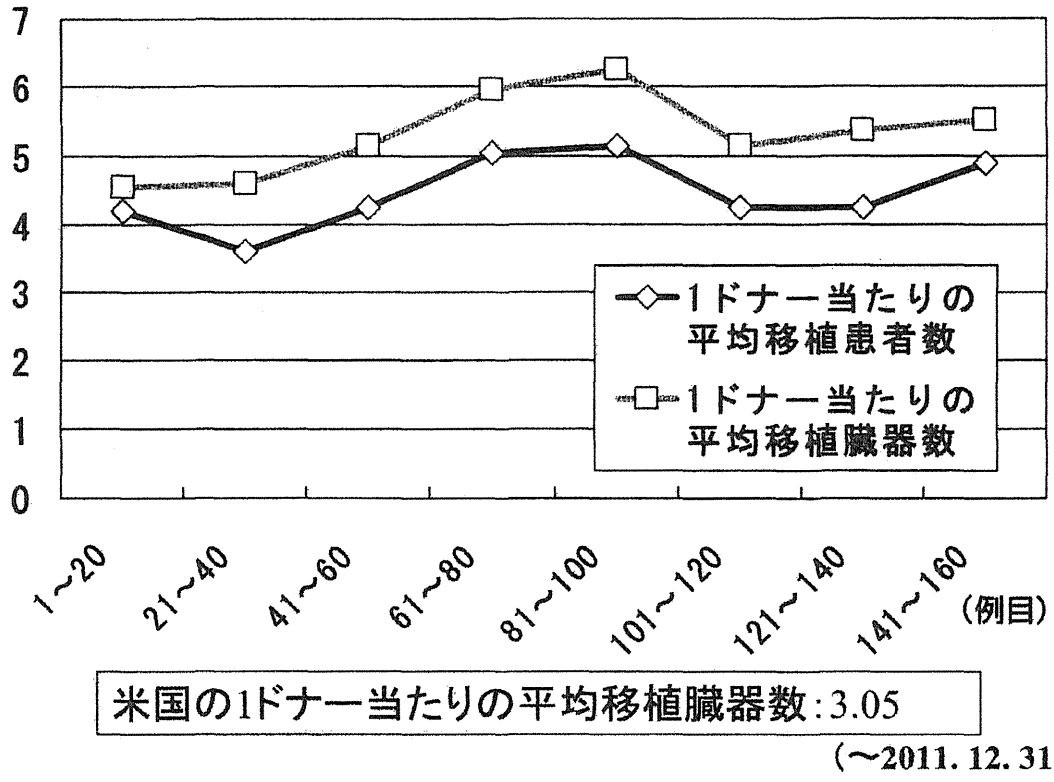


図４　膵臓移植待機登録者

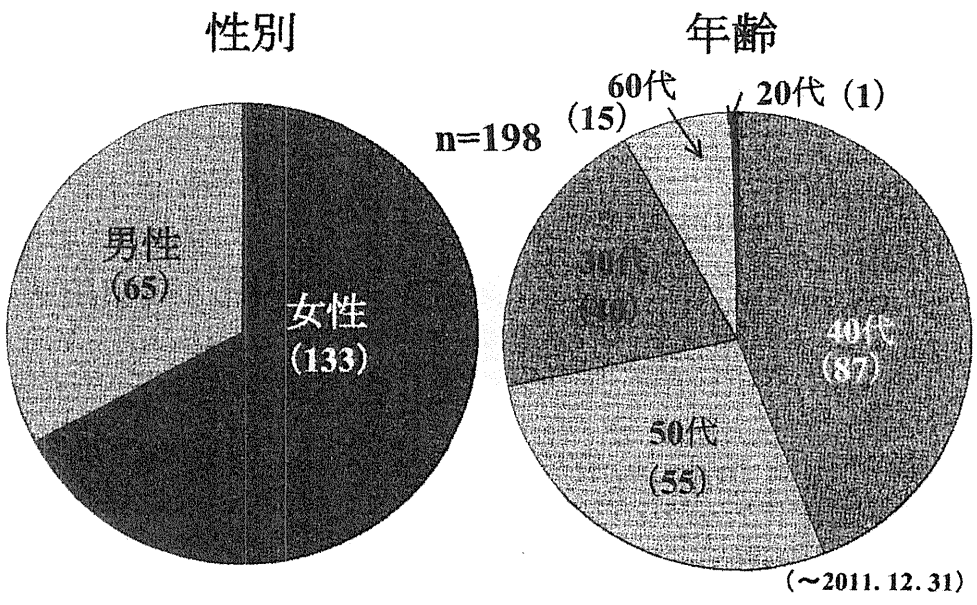
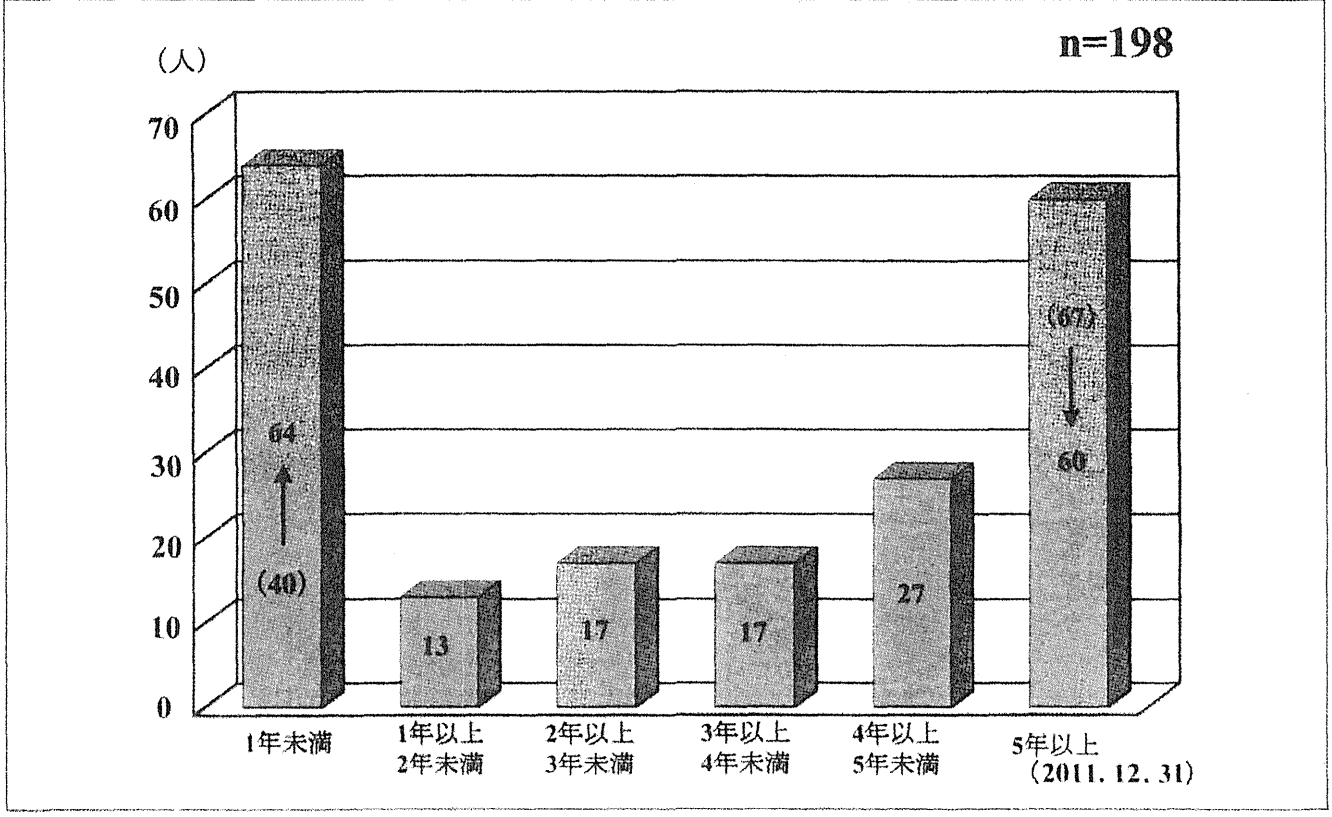


図5　膵臓移植登録者の待機期間



移植件数ならびに新規登録患者数の増加に伴ってやや改善傾向がみられる（**図5**）。しかしながら，待機期間中に，2011年末で35名が死亡し，また25名が糖尿病による重篤な合併症にて登録を抹消している。

2. 膵臓移植を受けたレシピエントについて

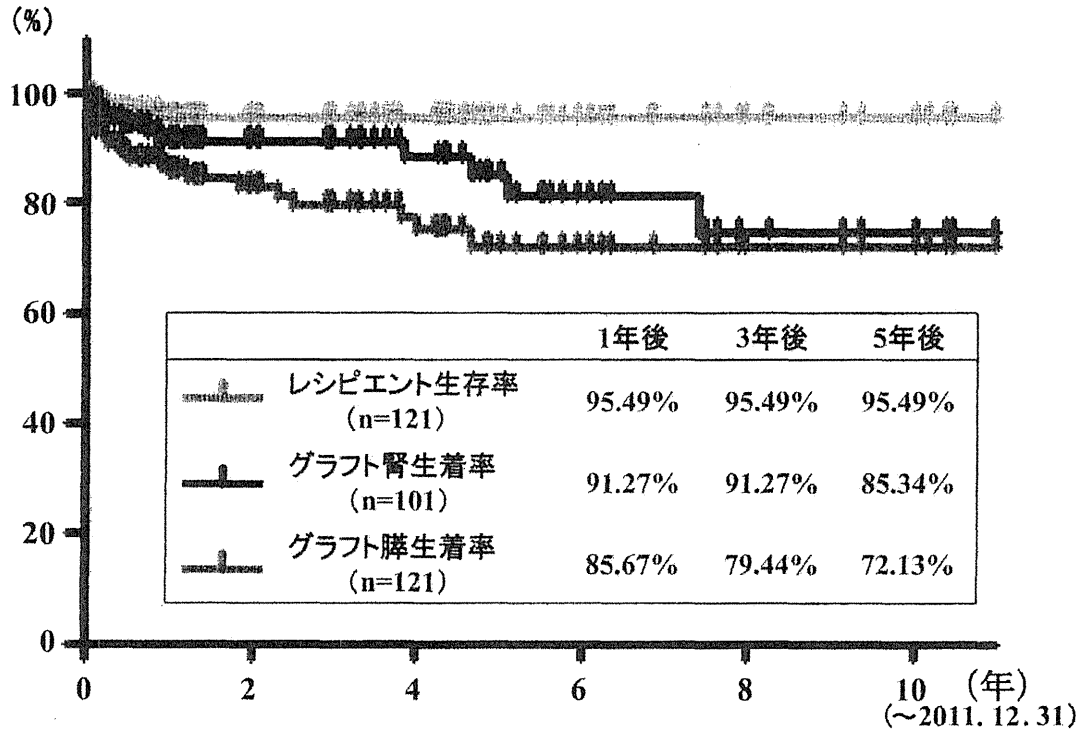
本邦での膵臓移植は，マージナルドナーであっても積極的に用いていることが特徴として挙げられる。Kapurらの定義[1]［①45歳以上，②不安定な血行動態（高用量のカテコラミンの使用），③心停止下ドナー］によると，本邦では約75%がマージナルドナーである[2]。

一方，欧米での膵臓待機レシピエント数は，肝臓や心臓のそれらとの相対的な割合から，臓器としての膵臓は余っており，余剰分は膵島あるいは研究用として使用されている。例えば，2006年の米国OPTN/SRTR（Organ Procure ment and Transplantation Network / Scientific Registry of Transplant Re cipients）のannual report[3]によれば，2005年の1年間で脳死ドナーのうち，65%の膵臓は摘出されなかった。19%（n＝1,442）の膵臓が摘出後移植された。また，5%は摘出されるも移植に至らなかった。2%は摘出され研究用に使用された。0.9%は膵臓移植として摘出されたが，膵島移植にまわされた。

臓器提供における肝・膵比率（ratio of liver to pancreas grafts）をみると，海外の主たるOPOs（Organ Procurement Organization）ならびに全米のOPOsにおいて，その比率は，それぞれ7.18，3.26と本邦の1.0に比して，かなり高いことがわかる。すなわち，海外では肝臓に比して，膵臓は積極的に摘出されていないことになる。これは，肝臓がlife saving organであるのに対して，膵臓移植の目的が腎臓移植と同様に，主として，QOLを追求する医療であると考えられているからである。しかしながら，Wisconsin大学などでは，selected，less-than-ideal donorを積極的に用いて，肝・膵比率を1.25まで引き下げ，良好な膵臓移植の成績を報告している[4]。

さて，本邦において，臓器移植法改正の前後で肝・膵比率をみてみると，改正前には1.05（67/64）であったのに対して，改正後は1.21（69/57）とやや増加傾向がみられた。これは移植症例の増加に伴って，各施設が移植の適応をより慎重に対処しているためと思わ

図6　膵臓移植後のレシピエント生存率とグラフト生着率



れた。

また，法改正前後でマージナルケースの数を比較してみると，改正前では64例中49例（76.6%）であったのに対して，改正後では57例中40例（70.2%）とやや低い傾向がみられた。急性期の合併症としての移植膵の血栓症については，改正前では5例（7.8%，マージナルは4例）みられたが，改正後は1例(1.8%，マージナル）であった。しかし，死亡例については改正前では1例（マージナル）であったのに対して，改正後には5例（マージナルはうち3例）と多い傾向があった。

2011年12月末での移植成績を示した（**図6**）。レシピエント生存率は95.5%，移植膵の生着率は1年，3年，5年でそれぞれ85.7%，79.4%，72.1%と症例数が増えても，以前と変わりない成績が得られている。この成績は欧米と比べて決して遜色ない結果と考えられる。

なお，本邦での膵臓移植におけるマージナルドナーに関する詳細については，本特集ならびに他稿[9]を参照されたい。

脳死下膵臓移植の今後

法改正を受けて，今後，脳死下での臓器移植は着実に症例数を増やしていくことが予想される。しかしながら，脳死の原因として脳血管障害が半数以上を占める本邦においては，マージナルドナーは避けて通ることができない関門であり，死戦期におけるさらなるドナー管理ならびに周術期のきめの細かい管理が要求されると思われる。

現在（2012年1月末日），日本臓器移植ネットワークに登録待機している患者の中で，膵臓待機者が198名に対し，腎臓単独待機者は12,523名と圧倒的に多く，その較差はすぐには解消しない。当面は，4類型の施設からの脳死下での臓器提供の促進に加えて，4類型以外の施設からの献腎の促進といったドナーアクションプランもこれまでと同様に進めていかねばならない。また，そうした中，現時点で2腎のうち，1腎が優先配分されている膵腎移植において，そのルールの見直しも検討されねばならないかもしれない。さらに，また近々再開される膵島移植との住み分けも考慮されなければならない。すなわち，心停止下で摘出された膵臓を用いる膵島移植では，献腎症例が少なくな

ることについて，症例数が確保できないのではないかといった懸念が生じる。したがって，脳死下での膵臓提供に際しても，高齢ドナーや肥満症例などの一定の条件付きで，膵島移植にまわすなどのルール作りが必要になることが予想される。

おわりに

本稿では，一昨年の臓器移植法の改正を受けて，脳死下での臓器移植が一気に増えたが，その前後で治療成績には大きな変化を認めなかったことを述べた。しかしながら，今後も条件の厳しいマージナルドナーが多くを占めていることには変わりはない。ドナー管理のみならずレシピエントの周術期管理をしっかりと行った上で，さらなる移植成績の向上のために障害となる因子を明らかにしていくことが今後ますます必要になってくる。

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Clin Transplant 2012: 26: E530–E535 DOI: 10.1111/ctr.12027

Clinical Transplantation

Acute kidney injury following living donor liver transplantation

Inoue Y, Soyama A, Takatsuki M, Hidaka M, Muraoka I, Kanematsu T, Eguchi S. Acute kidney injury following living donor liver transplantation.

Abstract: Background: Although acute kidney injury (AKI) is regarded as a frequent complication following deceased donor liver transplantation, the incidence of AKI following living donor partial liver transplantation (LDLT) has not yet been sufficiently investigated.
Patients and Methods: we used two definitions and investigated the influence of AKI on patient and graft survival. The definitions for the degree of AKI were as follows: AKI 1 was characterized by an increase in serum creatinine of 0.5 mg/dL, while AKI 2 was 1.0 mg/dL above the baseline within one wk during the post-operative course. The incidence and its impact were investigated.
Results: The incidence of AKI 1 was 63.1%. The development of AKI 1 was correlated with intra-operative blood loss ($p = 0.013$), the length of post-operative ICU stay, and hospitalization ($p = 0.020$ and 0.038). The incidence of AKI 2 was 27.7%, and AKI 2 was correlated with the length of both the post-operative ICU and hospital stays. The development of AKI 2 was significantly correlated with graft survival ($p = 0.015$).
Conclusion: Recognizing the peri-operative risk and development of AKI is important, because AKI post-LDLT is associated with a poorer graft survival and a possible worse long-term prognosis.

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Key words: acute kidney injury – calcineurin inhibitor – intra-operative hemorrhage – Model for End-Stage Liver Disease score – small-for-size graft

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Conflict of interest: The authors have no conflict of interest to declare.

Accepted for publication 27 June 2012

Because of the chronic donor shortage, LDLT and split liver transplantation have become common practices throughout the world. As a possible outcome of partial liver graft transplantation, small-for-size syndrome (SFSS) can occur if the partial liver graft volume is found to be insufficient for the recipient and frequently leads to death of recipient (1). The definition of SFSS is generally prolonged abnormal bile secretion, coagulopathy, and ascites within one wk after the operation. Difficulties in fluid management caused by persistent ascites are considered a possible risk of subsequent renal dysfunction. In addition, drug-induced renal injury is more common in patients with a fluid imbalance.

Acute kidney injury (AKI) is a frequent complication following deceased donor liver transplantation, and its incidence has been reported to range between 17% and 95% (2–5). However, thus far, the incidence of AKI following living donor liver transplantation (LDLT) has not been well investigated. The etiology of AKI post-liver transplantation is usually considered multifactorial, including surgery-related events, blood loss, hypotension, sepsis, the administration of a calcineurin inhibitor (CNI), volume depletion (5). In addition to these causes, in LDLT, it might be difficult to maintain an ideal fluid balance because of persistent massive ascites owing to a small-for-size graft. Renal dysfunction after LDLT may occur because of persistent portal hypertension and a hyperdynamic state in patients with a small-for-size graft (6, 7). Furthermore, renal dysfunction may also be present prior to transplantation because of hepatorenal syndrome or other factors such as infections or intravascular volume depletion (8–10). Therefore, an increase in serum creatinine is not uncommon post-liver transplantation.

In this study, we applied two definitions commonly used in the literature for AKI not requiring dialysis and evaluated the impact of these two types of AKI on patient outcome. We used different levels of severity of AKI and excluded AKI

requiring renal replacement therapy, as it has already been extensively studied. The purpose of this study was therefore to clarify the incidence of AKI post-LDLT and to determine its impact on the patient outcome.

Patients and methods

The sources of our data included chart review of our database of LDLT recipients who had undergone LDLT at Nagasaki University Hospital between April 2005 and November 2009 (n = 65). We reviewed our experience with AKI post-LDLT. The database has information regarding causes of liver disease, transplant or retransplant status, the Model for End-Stage Liver Disease (MELD) score, and intra-operative and post-operative clinical data. All patients were included in the study, regardless of their initial serum creatinine. Patients on dialysis prior to liver transplantation were excluded from the study. Definition of AKI is still controversial (3,11–13). For this study, we used two definitions commonly used in the literature to define AKI (14,15) and evaluated the influence of AKI on patient and graft survival based on these definitions. In addition, the selection of AKI definitions was made to represent the changes in renal function, from mild to more severe, occurring within one wk at any time during the hospitalization post-LDLT.

The two definitions for AKI were as follows: AKI 1 was characterized by an increase in serum creatinine of 0.5 mg/dL above the baseline (n = 41), while AKI 2 was characterized by an increase in serum creatinine of 1.0 mg/dL above the baseline (n = 18). These definitions were applied to serum creatinine levels obtained at regular intervals in the post-LDLT period. The baseline serum creatinine level is the one measured immediately prior to LDLT. Patients with AKI were compared to a control group without AKI. We investigated the risk factors of AKI. The association between AKI and graft survival, duration of ICU stay and hospital stay was investigated.

Immunosuppression and rejection

In patients with impaired renal function immediately before or after the transplant, the dose of CNI was limited (FK506: trough level 5–8 ng/mL, CyA: 100–150 ng/mL) or even temporarily withheld until renal function improves. If CNI is withheld, we generally used basiliximab to provide immunosuppression, in conjunction with MMF and prednisone, until the renal function improves and CNI can be started. Methylprednisolone was injected intravenously during surgery at a dose of 20 mg/kg and at a dose of 2–1 mg/kg/d tapered for one to six post-operative days, followed by oral prednisolone at 0.3 mg/kg/d (7–28 d), 0.2 mg/kg/d (after 28 d), and discontinued in three months to one yr after the procedure. If acute cellular rejection was observed, then bolus injections of methylprednisolone were administered in selected cases.

Pre-operative and post-operative data

Database information from pre-LDLT admission, intra-operative monitoring, and post-LDLT care was reviewed. The examined parameters included the patient age, gender, serum creatinine, MELD score, graft volume/standard liver volume ratio (GV/SLV ratio), sepsis, cytomegalovirus (CMV) and other infections, intra-operative blood loss, regimen of immunosuppressive drugs, causes of liver failure, length of hospital and intensive care unit (ICU) stay, and graft survival.

Statistical analysis

All categorical data were analyzed by a multivariate logistic analysis. p Values <0.05 were considered to be significant.

Results

The incidence of AKI was variable, depending on the definition applied for AKI. Tables 1 and 2 show the demographics and outcomes comparing the AKI patients with the control group.

Acute kidney injury 1 (an increase in serum creatinine of >0.5 mg/dL)

There was a higher incidence of AKI 1 (41/65 cases, 63.1%) compared with the incidence of AKI 2. The development of AKI 1 was associated with higher intra-operative blood loss ($p = 0.013$; Table 1). As a result, the relationship was observed between longer post-operative ICU stay ($p = 0.020$) and a longer overall hospital stay ($p = 0.038$ in comparison with the control group).

Acute kidney injury 2 (an increase in serum creatinine of >1.0 mg/dL)

The incidence of AKI 2 was 27.7% (18/65 cases). None of the factors was significant for the incidence of AKI.

Table 1. Description of patients with AKI 1 (Increase in serum creatinine of >0.5 mg/dL)

				Univariate logistic regression		
Criteria	Category	n	AKI 1	Odds	95% CI	p Value
Number		65	41 (63.1%)			
Age	<55	27	17 (63.0%)	Reference		
	≥55	38	24 (63.2%)	1.008	(0.363, 2.802)	0.987
MELD score	<15	27	16 (59.3%)	Reference		
	≥15	38	25 (65.8%)	1.322	(0.477, 3.663)	0.591
GV/SLV ratio	<38	32	19 (59.4%)	Reference		
	≥38	33	22 (66.7%)	1.368	(0.498, 3.760)	0.543
Sepsis	(−)	46	27 (58.7%)	Reference		
	(+)	19	14 (73.7%)	1.970	(0.607, 6.398)	0.259
CMV infection	(−)	41	25 (61.0%)	Reference		
	(+)	24	16 (66.7%)	1.280	(0.445, 3.678)	0.647
Intra-operative hemorrhage	<5000	30	14 (46.7%)	Reference		
	≥5000	35	27 (77.1%)	3.857	(1.328, 11.203)	0.013*
Pre-operative creatinine	<0.7	25	18 (72.0%)	Reference		
	≥0.7	37	21 (56.8%)	0.510	(0.172, 1.516)	0.226
	Unknown	3	2 (66.7%)	0.778	(0.060, 10.005)	0.847
Use of immunosuppressive	(−)	14	9 (64.3%)	Reference		
drugs (except CNI)	(+)	51	32 (62.7%)	0.936	(0.273, 3.207)	0.916
Use of immunosuppressive drugs	(−)	45	27 (60.0%)	Reference		
(except CNI from POD1)	(+)	20	14 (70.0%)	1.555	(0.504, 4.801)	0.442
Use of FK506	(+)	59	36 (61.0%)	Reference		
	(−)	6	5 (83.3%)	3.194	(0.350, 29.113)	0.303
LC-B	(−)	42	27 (64.3%)	Reference		
	(+)	23	14 (60.9%)	0.864	(0.303, 2.466)	0.785
LC-C	(−)	50	33 (66.0%)	Reference		
	(+)	15	8 (53.3%)	0.589	(0.183, 1.899)	0.375
LC-Alcoholic	(−)	59	37 (62.7%)	Reference		
	(+)	6	4 (66.7%)	1.189	(0.201, 7.034)	0.848

AKI, acute kidney injury; MELD score, Model for End-Stage Liver Disease score; GV/SLV ratio, graft volume/standard liver volume ratio; CMV, cytomegalovirus; CNI, calcineurin inhibitor; LC-B, cirrhosis caused by hepatitis B virus; LC-C, cirrhosis caused by hepatitis C virus; LC-Alcoholic, Alcoholic cirrhosis. *$p < 0.05$.

Length of post-operative ICU stay and post-operative hospital stay

The 58 patients were evaluated for factors associated with the length of their post-operative ICU stay. The development of AKI 1 and the MELD score were found to be related to the length of the post-operative ICU stay. The development of AKI 1, CMV infection, the use of an immunosuppressant other than a CNI at any time during the post-operative course, and the use of an immunosuppressant other than a CNI from POD1 were related to the length of the post-operative hospital stay. Because the patients of persistent poor graft function had died at an early stage, we excluded the patients from these examinations.

Causes of graft failure

The 65 patients were evaluated for the cause of their graft failure. The development of AKI 2 ($p = 0.015$), the patient's age ($p = 0.021$), and donor age ($p = 0.006$ in comparison with the control group) were all related to the graft survival (Table 3).

As a risk factor of AKI, the intra-operative hemorrhage was suggested. Acute kidney injury was related to the ICU stay, hospital stay, and graft survival.

Discussion

A high burden of chronic kidney disease (CKD) and end-stage renal disease (ESRD) post-liver transplantation have been reported; those are most frequently because of CNI-induced nephrotoxicity (16). AKI may occur more frequently in LDLT than in deceased donor liver transplantation (DDLT), because of the difficulties associated with fluid management and massive ascites production owing to SFSS, in addition to the nephrotoxicity of CNIs. In addition, other factors may contribute to the development of this complication (16, 17). AKI has been proposed to be an important risk factor for the long-term development of CKD and ESRD (17). Previous reports have shown evidence

Table 2. Description of patients with AKI 2 (Increase in serum creatinine of >1.0 mg/dL)

Criteria	Category	n	AKI 2	Univariate logistic regression		
				Odds	95% CI	p Value
Number		65	18 (27.7%)			
Age	<55	27	7 (25.9%)	Reference		
	≥55	38	11 (28.9%)	1.164	(0.384, 3.532)	0.789
MELD score	<15	27	9 (33.3%)	Reference		
	≥15	38	9 (23.7%)	0.621	(0.208, 1.856)	0.393
GV/SLV ratio	<38	32	9 (28.1%)	Reference		
	≥38	33	9 (27.3%)	0.958	(0.323, 2.841)	0.939
Sepsis	(−)	46	10 (21.7%)	Reference		
	(+)	19	8 (42.1%)	2.618	(0.830, 8.261)	0.101
CMV infection	(−)	41	12 (29.3%)	Reference		
	(+)	24	6 (25.0%)	0.806	(0.257, 2.526)	0.711
Intra-operative hemorrhage	<5000	30	7 (23.3%)	Reference		
	≥5000	35	11 (31.4%)	1.506	(0.498, 4.555)	0.468
Pre-operative creatinine	<0.7	25	8 (32.0%)	Reference		
	≥0.7	37	9 (24.3%)	0.683	(0.221, 2.108)	0.507
	Unknown	3	1 (33.3%)	1.063	(0.084, 13.517)	0.963
Use of immunosuppressive drugs	(−)	14	5 (35.7%)	Reference		
(except CNI)	(+)	51	13 (25.5%)	0.616	(0.174, 2.174)	0.451
Use of immunosuppressive drugs	(−)	45	12 (26.7%)	Reference		
(except CNI from POD1)	(+)	20	6 (30.0%)	1.179	(0.369, 3.769)	0.782
Use of FK506	(+)	59	15 (25.4%)	Reference		
	(−)	6	3 (50.0%)	2.933	(0.534, 16.125)	0.216
LC-B	(−)	42	10 (23.8%)	Reference		
	(+)	23	8 (34.8%)	1.707	(0.560, 5.198)	0.347
LC-C	(−)	50	18 (36.0%)	Reference		
	(+)	15	0 (0.0%)	<0.001	(<0.001, >999.999)	0.953
LC-Alcoholic	(−)	59	18 (30.5%)	Reference		
	(+)	6	0 (0.0%)	<0.001	(<0.001, >999.999)	0.971

AKI, acute kidney injury; MELD score, Model for End-Stage Liver Disease score; GV/SLV ratio, graft volume/standard liver volume ratio; CMV, cytomegalovirus; CNI, calcineurin inhibitor; LC-B, cirrhosis caused by hepatitis B virus; LC-C, cirrhosis caused by hepatitis C virus; LC-Alcoholic, Alcoholic cirrhosis.

that AKI is not a transient phenomenon, but a complication that may have long-lasting implications on long-term outcomes, including mortality (11, 12).

We hypothesized that the incidence of AKI following LDLT would be higher than that after deceased donor liver transplantation with a whole liver. Although 30 or more definitions of AKI have been advocated so far, the parameters most frequently used for the diagnosis of AKI are the creatinine level and the volume of urine. A better definition for early and less severe forms of AKI will assist in designing studies to prevent this complication. The ideal definition of AKI is controversial. In this study, AKI was diagnosed according to the development of a rapid increase in creatinine, which seemed to be a useful and convenient definition for the patient grouping and data collection.

In the analysis of the risk factors for AKI 1, a larger amount of intra-operative blood loss (≥5000 mL) was significantly associated with the incidence of AKI 1. Decreased renal blood flow because of intra-operative major blood loss is considered a cause of AKI 1. Neither the MELD score nor the GV/SLV ratio significantly affected the development of AKI 1. It was suggested that AKI can be avoided by appropriate management after surgery, even in the patients with a high pre-operative MELD score or a low GV/SLV ratio, who are generally thought to be a group at high risk for AKI. Also, the type of immunosuppressant administered was not correlated with the development of AKI 1. This was thought to be a result of recognizing the high-risk group pre-operatively and selecting an appropriate choice of the post-operative immunosuppressant. The MELD score and GV/SLV ratio were also not significant factors associated with the development of AKI 2.

The patients with AKI 1, CMV infection, and who used an immunosuppressant other than a CNI had an extended post-operative hospital stay. In particular, the patients administered an immunosuppressant other than a CNI from POD1 were more likely to have an extended post-operative hospital stay. The patients with AKI 1 and a high pre-operative MELD score (≥15) required an extended post-operative ICU stay. The

Table 3. Univariate risk factors for graft failure

Criteria	Category	n	Graft failure	Univariate logistic regression		
				Odds	95% CI	p Value
Number		65	15 (23.1%)			
AKI 1	(−)	24	3 (12.5%)	Reference		
	(+)	41	12 (29.3%)	2.90	(0.726, 11.562)	0.132
AKI 2	(−)	47	7 (14.9%)	Reference		
	(+)	18	8 (44.4%)	4.57	(1.338, 15.616)	0.015*
Age	<55	27	2 (7.4%)	Reference		
	≥55	38	13 (34.2%)	6.500	(1.327, 31.829)	0.021*
Age of donor	<55	42	5 (11.9%)	Reference		
	≥55	23	10 (43.5%)	5.692	(1.638, 19.782)	0.006**
MELD score	<15	27	5 (18.5%)	Reference		
	≥15	38	10 (26.3%)	1.571	(0.469, 5.269)	0.464
GV/SLV ratio	<38	32	8 (25.0%)	Reference		
	≥38	33	7 (21.2%)	0.808	(0.254, 2.567)	0.717
Sepsis	(−)	46	8 (17.4%)	Reference		
	(+)	19	7 (36.8%)	2.771	(0.831, 9.239)	0.097
CMV infection	(−)	41	8 (19.5%)	Reference		
	(+)	24	7 (29.2%)	1.699	(0.527, 5.479)	0.375
Intra-operative hemorrhage	<5000	30	7 (23.3%)	Reference		
	≥5000	35	8 (22.9%)	0.974	(0.306, 3.096)	0.964
Pre-operative creatinine	<0.7	25	5 (20.0%)	Reference		
	≥0.7	37	10 (27.0%)	1.481	(0.438, 5.015)	0.528
	Unknown	3	0 (0.0%)	<0.001	(<0.001, >999.999)	0.981
Use of immunosuppressive drugs (except CNI)	(−)	14	2 (14.3%)	Reference		
	(+)	51	13 (25.5%)	2.053	(0.405, 10.414)	0.385
Use of immunosuppressive drugs (except CNI from POD1)	(−)	45	9 (20.0%)	Reference		
	(+)	20	6 (30.0%)	1.715	(0.515, 5.712)	0.380
Use of FK506	(+)	59	12 (20.3%)	Reference		
	(−)	6	3 (50.0%)	3.917	(0.700, 21.901)	0.120
LC-B	(−)	42	11 (26.2%)	Reference		
	(+)	23	4 (17.4%)	0.593	(0.165, 2.132)	0.424
LC-C	(−)	50	11 (22.0%)	Reference		
	(+)	15	4 (26.7%)	1.289	(0.342, 4.854)	0.707
LC-Alcoholic	(−)	59	15 (25.4%)	Reference		
	(+)	6	0 (0.0%)	<0.001	(<0.001, >999.999)	0.973

AKI, acute kidney injury; MELD score, Model for End-Stage Liver Disease score; GV/SLV ratio, graft volume/standard liver volume ratio; CMV, cytomegalovirus; CNI, calcineurin inhibitor; LC-B, cirrhosis caused by hepatitis B virus; LC-C, cirrhosis caused by hepatitis C virus; LC-Alcoholic, Alcoholic cirrhosis. *$p < 0.05$; **$p < 0.01$.

development of AKI 2 was not associated with either the ICU stay or the total hospital stay. In contrast to AKI 1, the reason why AKI 2 did not influence the ICU or hospital stay needs further investigation.

The risk factors for graft failure included AKI 2, the age of the recipient (≥ 55), and the age of the donor (≥ 50). Acute kidney injury 1 was not recognized as a risk factor for graft failure. In orthotopic liver transplantation, an increase in creatinine of 0.5 or more in a short period of time has been reported to deteriorate the survival of the graft and the patient. Similarly, in this study, a creatinine increase of 1.0 or more was associated with decreased long-term survival of the graft; therefore, early intervention by recognizing the group at high risk for AKI is considered important in the post-operative management of LDLT. Some authors have reported that a creatinine increase of about 0.3 also influences the prognosis (13, 14). Furthermore, AKI has been reported to be associated with the prognosis after five yr (15). In the intensive care area, it is important to recognize AKI even if it is characterized by a low-grade increase in creatinine, because AKI increases the mortality rate. Because an increase in creatinine in the normal range is a marker of the cardiovascular events (18), increased creatinine in hypertensive patients is a marker of the blood vessel disease (19). Therefore, it is also possible that in the LDLT patients, AKI could be a sign of pre-existing blood vessel disease or a possible cardiovascular event that could affect the long-term survival.

In conclusion, recognizing the risk and development of AKI is important, although a variety of diagnostic criteria still exist, because AKI post-LDLT is associated with a decreased graft survival and a possible long-term unfavorable outcome.

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Surg Today (2012) 42:816–818
DOI 10.1007/s00595-012-0168-y

HOW TO DO IT

Prevention of gastric stasis by omentum patching after living donor left hepatectomy

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Received: 17 March 2011 / Accepted: 15 August 2011 / Published online: 27 March 2012

Abstract Among 137 living liver donors who underwent partial hepatectomy between August 1997 and November 2010, 58 donated the left lobe of their liver, with or without the caudate lobe. Gastric stasis developed after surgery in 4 (7 %) of these 58 donors (Fig. 1); possibly because of dislocation of the stomach after hepatectomy and adhesion between the stomach and the cut surface of the liver. This complication is specific to left hepatectomy [1] and although not life-threatening, it is symptomatic and requires endoscopic or surgical intervention. We describe our surgical technic designed to prevent this complication.

Keywords Liver transplantation · Living donor · Omentum

Surgical procedures (Fig. 2)

After left hepatectomy, there is a large cavity between the stomach and the cut surface of the liver (Fig. 2a). A closed suction drain is generally placed along the cut surface via the dorsal route of the hepatoduodenal ligament. Our method involves stretching the omentum fully (Fig. 2b) into this space, covering the hepatoduodenal ligament and the cut surface of the liver (Fig. 2c), ensuring that the stomach and transverse colon are left in their natural positions. We simply leave the omentum in place without suturing (Fig. 2d). Patients with gastric stasis vomit frequently because their stomach is enlarged, as can be seen on abdominal X-ray and/or computed tomography images (Fig. 1). Computed tomography is performed routinely 1 month after surgery, mainly to check the regeneration of the liver.

We performed omental patching in the most recent 45 of the 58 donors who underwent left partial hepatectomy. The incidence of gastric stasis decreased significantly from 23 % (3/13) in the first 13 patients to 2 % (1/45) in the last 45 ($P < 0.05$; Fisher's test). Computed tomography after surgery confirmed that the omentum was still in place between the stomach and the liver (Fig. 3a), preventing adhesion between them in all except one patient, in whom gastric stasis was possibly caused by dislocation of the omentum. All 3 of the former 13 patients with gastric stasis after surgery without omentum patching were observed to have tight adhesion between the stomach and the cut surface of the liver (Fig. 3b).

Gastric stasis is not life-threatening, but it impairs the quality of life of living liver donors. In left hepatectomy, the stomach is twisted and falls into the space after the liver lobe is removed. This leads to adhesion between the stomach and the cut surface of the liver. None of the 62 patients who underwent right hepatectomy during the same period in this series suffered any gastric stasis. Although all four of our patients who suffered gastric stasis are now doing well, three required endoscopic repair, and one required surgical adhesiolysis. There are few studies on the prevention of gastric stasis after left hepatectomy. Yoshida et al. [2] proposed a procedure for fixing the greater omentum to the peritoneum to prevent the stomach from falling into the space after hepatectomy. We devised omentum patching because it is simple and requires no artificial materials. A sodium hyaluronate and carboxymethylcellulose membrane was recently introduced as an

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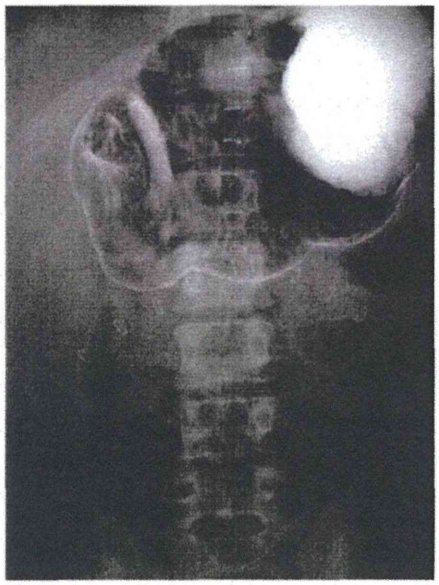

Fig. 1 Gastric stasis after living donor left hepatectomy. Fluorescent imaging study shows an enlarged stomach with no passage of radiofluorescence through the pylorus

effective material to prevent bowel obstructions being caused by adhesions [3, 4], but it is not clear whether it can be used to prevent adhesions between the cut surface of the liver and the stomach. Besides the omentum, another intra-abdominal material that could possibly be used is intestine, but this might lead to bowel obstruction due to adhesion. We simply left the omentum without any plasty in the space between the stomach and the cut surface of the liver, and without sutures. Even though it was not fixed, computed tomography confirmed that the omentum remained in place between the stomach and the liver in most of the patients. The omentum is used widely to prevent or treat various morbidities, including anastomotic leakage of the colon [5], perforation of a duodenal ulcer [6], hepatic hydatid cyst [7], and in some thoracic surgery [8]. It is generally used with some kind of plasty, but we simply placed it over the area without any plasty or sutures, and thus named the procedure as "omentum patching". This procedure cannot be applied if the omentum is too small to cover the cut surface of the liver, or if there are intra-abdominal adhesions involving the omentum from prior laparotomy. In our series, omentum patching was carried out easily in all patients, except for one who had previously undergone colectomy. We believe that the vast majority of living liver donors are candidates for omentum patching at the time of hepatectomy because they are healthy volunteers. This procedure is also useful for patients undergoing left hepatectomy for neoplasms, but it is more applicable in living donor hepatectomy, in which any complications, even minor ones, should be avoided.

One possible disadvantage of this procedure is that it may leave the person susceptible to severe peritonitis if intra-abdominal inflammation, such as appendicitis, occurs after surgery, because the general functions of the omentum include migration, covering, adhesion, and mending the absorption against peritoneal injury or infection. None of our patients have experienced any such adverse events

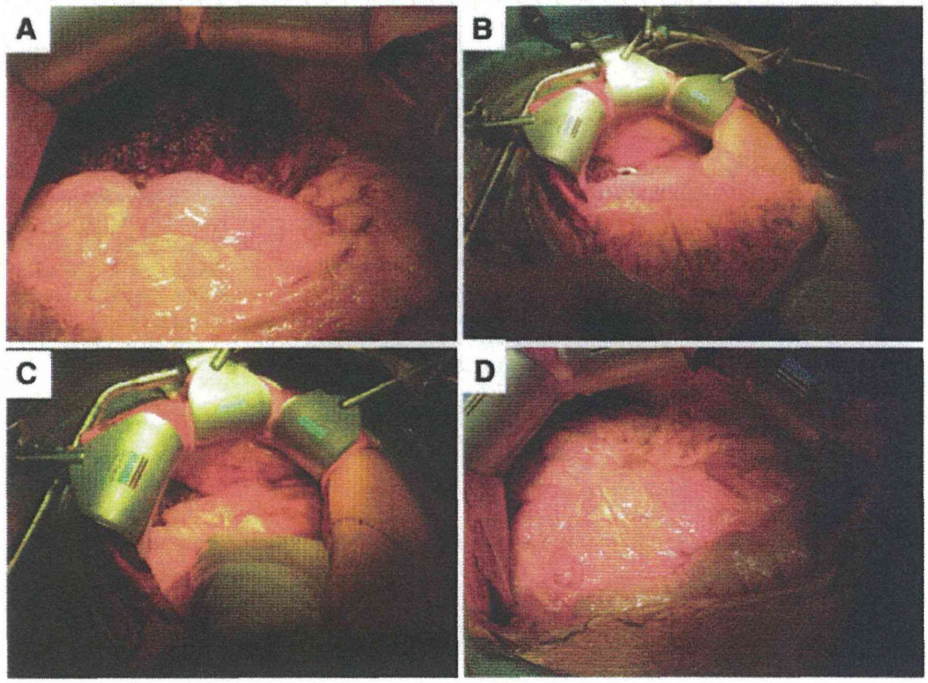

Fig. 2 Surgical procedure for omentum patching. There is a large cavity between the stomach and the cut surface of the liver (**a**). The omentum is fully stretched (**b**) and placed over the hepatoduodenal ligament and the cut surface of the liver (**c**). The omentum is left in place without sutures (**d**)

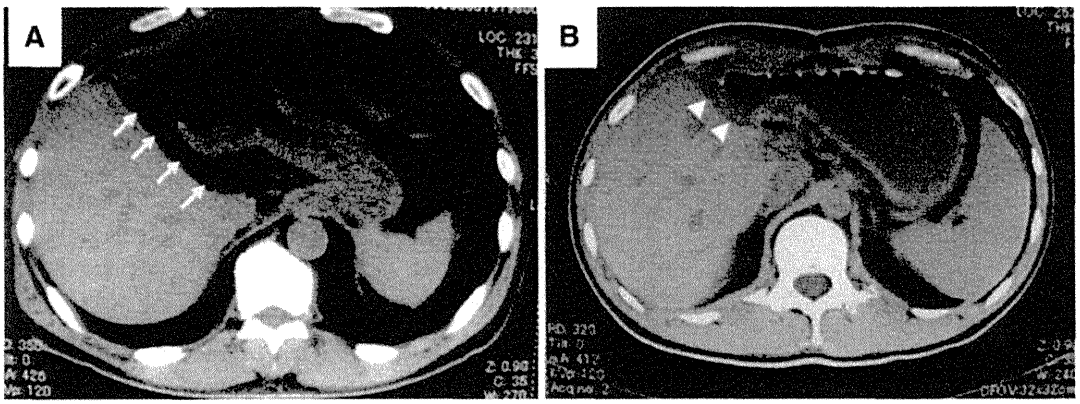

Fig. 3 Computed tomography scan after surgery with (**a**) and without (**b**) omentum patching. After omental patching, the omentum remains in place between the stomach and the cut surface of the liver (*arrows*, **a**), whereas without omental patching, there are tight adhesions in a person suffering from gastric stasis (*arrowheads*, **b**)

within a median follow-up period of 16 months (range 1–42 months). Another possible cause of adhesion between the stomach and the cut surface of the liver is bile leakage. Thus, it is essential to cut the bile duct at an adequate point [9]. There were no cases of bile leakage causing tight adhesion in our series, as we cut the bile duct at the optimal cutting point during donor surgery using C-arm cholangiography [10].

In conclusion, although a randomized study should be done, the findings of this series demonstrate that omentum patching prevents gastric stasis after living donor left hepatectomy.

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J Hepatobiliary Pancreat Sci (2012) 19:379–381
DOI 10.1007/s00534-011-0424-3

ORIGINAL ARTICLE

Use of stepwise versus straightforward clamping of biliary drainage tubes after living-donor liver transplantation: a prospective, randomized trial

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Published online: 30 July 2011

Abstract
Background/purpose There has been no report describing the optimal clamping method for biliary drainage tubes in living-donor liver transplantation (LDLT), although biliary splinting and drainage plays an important role in this procedure.
Methods When performing LDLT, we generally use a 2-mm drainage tube for the splint at the biliary anastomosis, and externalize it through the lower common bile duct. In the present study, when the serum levels of total bilirubin were lower than 5 mg/dl, and negativity for biliary complications and good passage of contrast media to the duodenum were confirmed, the drainage tubes were clamped. To determine the optimal clamping method, patients were randomly divided into two groups; those whose drainage tubes were subjected to stepwise clamping for 3, 6, 12, and 24 h per day ($n = 20$), and those whose drainage tubes were subjected to straightforward clamping ($n = 20$).
Results The results of liver function tests and rates of clamping failure were not different between the two groups after the different clamping methods were used.
Conclusions Straightforward clamping could be a simple and reasonable method to close a biliary drainage tube after LDLT.

Keywords Clamp · Liver transplantation · Biliary drainage · Tube

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Introduction

Biliary drainage and splinting plays an important role in living-donor liver transplantation (LDLT) because the rate of biliary complications is higher in LDLT than in deceased-donor whole LT [1, 2]. We generally use an external biliary splint and have previously reported the two-step method used for removal of the splint [3].

Anecdotally, a stepwise clamping method has sometimes been preferred to straightforward clamping to train the sphincter of Oddi in the papilla of Vater after decompression through the drainage tube following LT. The preference for the stepwise method is due to concerns that straightforward clamping may lead to dysfunction of the sphincter of Oddi after long-term decompression through the stent tube. However, it is not known whether stepwise clamping truly yields a better outcome, and there has been no report examining this matter in LT.

We investigated 40 LDLT patients who were randomly allocated to two groups in which different methods were used for clamping the biliary drainage tube.

Methods

Patients

Of 66 patients in whom we performed liver transplantations between May 2006 and October 2009, 65 were adult-to-adult LDLTs. Of these 65, 40 patients who underwent duct-to-duct biliary reconstruction with a tube splint at the anastomotic site and survived beyond 3 months were included in this study. This prospective randomized control study was conducted with the permission of the institutional ethics committee. Six ABO-incompatible patients

received a single dose of rituximab 1 week prior to the LDLT [4].

Biliary drainage tube placement

As reported previously, we used a polyvinyl chloride tube of 2-mm diameter, which was originally used for retrograde transhepatic biliary drainage, for our LDLT patients [3]. The tube was equipped with a malleable metallic dull-tipped splint at one end. Prior to the performance of duct-to-duct biliary anastomosis, the metallic splint of the tube was inserted from the lumen of the recipient's side of the hepatic duct and externalized through the common bile duct above the upper edge of the duodenum. Subsequently, duct-to-duct anastomosis was performed with interrupted sutures of 6-0 polydioxanone, and the tube was placed inside the graft intrahepatic bile duct for decompression and splinting. After the tube placement, the externalized site of the common bile duct was treated with purse-string sutures of 6-0 polydioxanone. Ductoplasty was performed in 4 patients with a right lobe graft; in 3 of these patients two tubes were placed, one in the anterior and one in the posterior branches of the bile duct. In the other patient with a right lobe graft, two tubes were placed when anterior and posterior branches of the bile ducts were too distant to perform ductoplasty.

Groups

When the serum levels of total bilirubin were lower than 5 mg/dl, and negativity for any biliary complications (leakage or severe stricture) and a good passage of contrast media to the duodenum were confirmed by fluoroscopic study, an attempt to clamp the biliary drainage tube was initiated 1 day after the fluoroscopic study. The following two methods were used for the clamping: for stepwise clamping ($n = 20$), the drain tube was clamped for 3 h on day 1, 6 h on day 2, 12 h on day 3, and 24 h per day thereafter. After each temporary clamping, the biliary drainage tube was opened and externally drained. For the straightforward clamping ($n = 20$), the drain tube was clamped and remained closed.

After the clamping, liver function tests (T. Bil: total bilirubin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyl transpeptidase) were performed on days 1 and 3. During the clamping period, the patients continued to eat hospital meals three times a day.

Statistics

All data were expressed as median values with ranges. Statistical analysis was performed using the Mann–Whitney *U*-test for continuous values. Statistical significance was defined as a p value of <0.05. The StatView 5.0 software program (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analyses.

Table 1 Patient characteristics and liver function tests after the clamping

	Stepwise ($n = 20$)	Straightforward ($n = 20$)	
Age (years)	56 (31–67)	57 (33–68)	n.s.
Gender (M:F)	13:7	13:7	n.s.
Graft type (right-side graft:left-lobe graft)	10:10	10:10	n.s.
Bile ductoplasty	3	1	n.s.
Double tubes	3	0	n.s.
ABO-incompatible	1 (5%)	5 (20%)	n.s.
Starting day of the clamping	22 (12–54)	29 (9–59)	n.s.
T. Bil before clamping (mg/dL)	1.9 (0.6–5.6)	2.0 (0.6–11.1)	n.s.
After 1 day	1.9 (0.5–5.4)	1.8 (0.7–9.6)	n.s.
After 3 days	1.5 (0.5–4.6)	1.5 (0.4–7.2)	n.s.
ALT before clamping (IU/L)	73 (24–177)	89 (5–537)	n.s.
After 1 day	67 (21–178)	80 (7–567)	n.s.
After 3 days	60 (16–177)	81 (8–542)	n.s.
ALP before clamping (IU/L)	377 (115–1,744)	369 (176–1,100)	n.s.
After 1 day	382 (136–1,736)	377 (107–1,260)	n.s.
After 3 days	345 (138–1,698)	380 (169–1,410)	n.s.
GGT before clamping (IU/L)	94 (13–368)	100.5 (17–538)	n.s.
After 1 day	113 (17–358)	150 (16–549)	n.s.
After 3 days	94.5 (14–365)	100 (16–577)	n.s.

Numbers in parentheses are ranges, unless otherwise indicated. *n.s.* not significant, *T. Bil* total bilirubin, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma glutamyl transpeptidase

Results

Table 1 shows the characteristics of the patients in the study. There were no statistically significant differences in age, gender, graft type, the starting day of clamping after LDLT, or ABO incompatibility between the groups.

At the time of the clamping, there were also no significant differences between the groups in the serum levels of T. Bil, ALT, ALP, and GGT. After each type of clamping of the biliary drainage tube, there were no significant differences between the groups in the serum levels of total bilirubin, AST, ALP, or GGT on days 1 and 3. There was no clamping failure in either of the groups.

Discussion

In the present study, we demonstrated that there were no differences in the patient outcomes after using the stepwise versus the straightforward clamping method for the biliary drainage tube after LDLT.

Biliary splinting plays an important role in LDLT, as the rate of biliary complications is higher in LDLT than in deceased-donor whole LT [1, 2]. We generally use a 2-mm tube for stenting at the biliary anastomosis, externalize it through the lower common bile duct, and fistulize it using the duodenal serosa [3]. The safety of the two-step procedure for removal of the splint tube was reported previously by our group [3]. In order to clarify the effects of the stepwise clamping method, we performed the present prospective study.

In our patients, there were no differences between the groups in the distribution of graft type, i.e., right lobe grafts, right posterior grafts, and left lobe grafts. After the clamping, we observed no differences between the outcomes in the patients treated using the two different clamping methods. In addition, in our subgroup analysis of graft type within each group, there were no significant differences in any of the parameters. Moreover, ABO-incompatible patients did not show any additional response after clamping of the biliary drainage tube, regardless of the clamping method used.

In one patient, we started to clamp the tube when the level of total serum bilirubin was still more than 5 mg/dl because of a lack of any biliary complications at 2 months after LDLT. However, there was no increase in any of the examined parameters in this patient in the straightforward clamping group.

Studies on the duration of clamping procedures have been performed only in the area of total knee arthroplasty [5–8]. In one of these studies, a reduction of blood loss was confirmed when 1-h clamping was applied as compared to a 4-h clamping method [5]. However, there has been no previous report describing the clamping method or duration of use for a biliary drainage system; therefore, even specialists in this field sometimes adopt the conventional stepwise method after LDLT.

In conclusion, we performed a randomized control study to examine differences arising due to the use of different clamping methods. Our results indicate that the straightforward clamping method could be a simple and reasonable method to successfully close biliary drainage tubes after LDLT.

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