Systematic review and meta-analysis of studies of biliary reconstruction in adult living donor liver transplantation

Short title: **Biliary reconstruction in adult LDLT**

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ABSTRACT

Background: The chance of biliary complication after living donor liver transplantation (LDLT) is considerable.

Objective: To investigate the impact of biliary reconstruction method on post-LDLT biliary complications.

Data sources: PubMed and Web of Science.

Review methods: A systematic search was conducted using the search term "[biliary complications] OR [biliary complication] OR [biliary stricture] OR [bile leak] AND [living donor liver transplantation]". Cross-referencing was allowed so as to encompass more potentially relevant studies. All English papers on adult LDLT published between 1990 and 2014 were considered for review. Papers focusing on biliary reconstruction method in relation to post-LDLT biliary complications were included.

Results: The meta-analysis recruited six retrospective studies but no randomised trial or prospective study. The six studies covered 1286 patients with 260 cases (20.2%) of biliary anastomotic stricture and 118 cases (9.2%) of biliary leakage. For biliary reconstruction, 365 patients (28.4%) underwent hepaticojejunostomy and 909 (70.7%) underwent duct-to-duct anastomosis, while 12 (0.9%) underwent both and were thus excluded from analysis. A lower rate of biliary anastomotic stricture was found in patients with hepaticojejunostomy compared with patients with duct-to-duct anastomosis (Mantel-Haenszel odds ratio 0.448, 95% confidence interval 0.311-0.643; p=0.000). Rates of biliary leakage were similar in the two groups (Mantel-Haenszel odds ratio 1.27, 95% confidence interval 0.821-1.966; p=0.283).

Conclusion: In the comparison of hepaticojejunostomy and duct-to-duct anastomosis in adult LDLT, the latter was found to be associated with a bigger chance of biliary anastomotic stricture but not biliary leakage.

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INTRODUCTION

Living donor liver transplantation (LDLT) has the most significant impact in Asia, where the issue of organ shortage is most extreme. The availability of LDLT to adult patients has provided the driving force for a drastic increase in cases of LDLT in recent years. The number of LDLTs performed in Asia each year has increased tremendously. LDLT comprises more than 90% of liver transplants in Asia (1, 2). In Korea, more than 80% of liver grafts are from living donors (3). In Hong Kong, about half of the liver transplants are LDLTs, most of which (around 90%) use the right liver lobe.

LDLT is one of the most complicated and technically demanding surgical procedures and often entails high morbidity and reoperation rates (4), but with advances in techniques and management in recent years, an excellent graft survival rate of over 90% can be achieved even in high-risk recipients (5). Nonetheless, post-LDLT biliary complications, namely biliary leakage (BL) and biliary stricture, are still a major problem that affects long-term transplant outcomes and quality of life, and is occasionally the cause of graft loss or patient death.

Duct-to-duct anastomosis (DDA) and hepaticojejunostomy (HJ) are the two most common methods of bile duct reconstruction in LDLT. DDA is gaining popularity over HJ because it needs a shorter operation time, causes fewer septic complications, leaves patients with better physiologic enteric function, and allows easier endoscopic access to the biliary tract in case of future need (6). However, biliary complications after DDA are still a challenging problem; the incidence is around 20% at our centre (7). Moreover, an association between this technique and postoperative biliary stricture has been suggested (7, 8). The incidence of post-DDA biliary stricture in recipients of liver grafts from living donors is consistently higher when compared with recipients of whole liver grafts (9). This might be related to the blood supply of the anastomosis, the presence of multiple small-caliber donor

ducts, or technical flaws (10). Biliary anomaly in grafts may also give rise to biliary complications in recipients.

Jeon et al. (11) reported two significant risk factors for biliary complications in LDLT, namely, a short right bile duct and a long caudal segment of the right posterior bile duct of donor. A single-centre retrospective study reported that whether DDA or HJ was used did not significantly influence the incidence of biliary anastomotic stricture (BAS) in adult LDLT using the right liver lobe (7). Nonetheless, whether bile duct reconstruction method in LDLT has any significant impact on the development of biliary complications is still open to question. And this triggered the systematic review and meta-analysis reported in this paper.

METHODS

The study was conducted according to the guidelines proposed by the Meta-analysis of Observational Studies in Epidemiology group (12).

Search Strategy

A systematic search was conducted on the PubMed database and Web of Science, using the search term “[biliary complications] OR [biliary complication] OR [biliary stricture] OR [bile leak] AND [living donor liver transplantation]”. Cross-referencing was allowed so as to encompass more potentially relevant studies.

Inclusion and Exclusion Criteria

All studies on adult LDLT published in English between 1990 and 2014 were considered for review. Papers focusing on bile duct reconstruction method in relation to post-LDLT biliary complication were included. Key variables included were number of recipients, method of bile duct reconstruction (DDA or HJ), incidence of BAS, incidence of

BL, and treatment modality. Identified variables were entered into a database for subsequent statistical analysis.

Definitions

BAS was deemed present if the diameter of a biliary anastomosis was <50% of the diameter of the graft bile duct on endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography, or if overt proximal ductal dilatation was seen on computed tomography or ultrasonography (8). Patients with non-anastomotic or ischaemic-type biliary strictures (related to ABO-incompatible liver transplantation or manifested as hepatic artery thrombosis, recurrence of primary sclerosing cholangitis, or acute or chronic rejection) were excluded from analysis.

If a patient had one of the following three conditions after liver transplantation, BL was deemed present: (A) Bile was collected through an abdominal drain. (B) Intra-abdominal collection containing frank bile or bile-stained fluid was present and required drainage. (C) Active contrast leakage via the external-internal splintage tube was present on ERC or cholangiography (13).

Statistical Analysis

The software Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) was used to formulate corresponding figures and generate forest plots. Pearson's chi-squared test or Fisher's exact test was used to compare categorical variables. Nonparametric continuous variables were compared by the Mann-Whitney U test and presented as means with standard deviation (or medians with or without range). Parametric continuous variables were compared by Student's t test and presented as means with standard deviation. P values <0.05 were regarded as statistically significant and all p values were two-tailed.

RESULTS

After the systematic search, 16 papers were identified as eligible for review (7, 8, 14-27). Figure 1 shows the search process and the number of papers excluded with reasons for exclusion. No randomised controlled trial was found. Cross-referencing did not reveal further papers.

Six studies were recruited, covering 1286 adult LDLTs given to the same number of patients. For bile duct reconstruction, 909 patients (70.7%) underwent DDA only and 365 patients (28.4%) underwent HJ only, while 12 patients (0.9%) underwent both. There were 260 cases (20.2%) of BAS and 118 cases (9.2%) of BL. Table 1 is a summary of data from the six studies. Totally 1274 patients were included for analysis after 12 patients (8 in the study by Kasahara et al. (19) and 4 in the study by Hwang et al. (8)) who underwent both DDA and HJ were excluded. In the analyses of BL and overall biliary complication, the study by Seo et al. (21) containing 239 patients (217 with DDA and 22 with HJ) was excluded since it made no breakdown of the 15 cases of BL therein according to bile duct reconstruction method. As a result, there were 259 cases of BAS (20.3% of 1274 patients) and 101 cases of BL (9.8% of 1035 patients) in our analysis.

ERC, percutaneous transhepatic biliary drainage (PTBD) and surgery (surgical revision or retransplantation) were the three modalities adopted for the management of BAS and BL. ERC was always the first-line treatment if bile duct reconstruction was done with DDA. BAS was successfully managed by ERC in 56 patients (21.5%), by PTBD in 116 patients (44.4%), by ERC+PTBD in 18 patients (6.9%), by surgical revision in 64 patients (24.5%), and by retransplantation in 2 patients (0.7%). Treatment for BAS in 3 patients was not specified. BL was successfully managed by ERC in 12 patients (10.3%), by PTBD in 24 patients (20.7%), by ERC+PTBD in 2 patients (1.7%), and by surgical revision in 62 patients (55.2%).

Treatment for BL in 1 patient was not specified. No retransplantation was performed for BL. There was no mortality directly related to BAS or BL.

When patients with DDA were compared with patients with HJ, it was found that the former had significantly higher rates of overall biliary complication (31.6% vs. 21.6%; p=0.001) and BAS (23.9% vs. 11.5%; p<0.001) but not BL (9.4% vs. 10.5%; p=0.104) (Table 2). Figure 2 is a forest plot for BAS. The incidence of BAS was significantly lower among patients with HJ (Mantel-Haenszel odds ratio 0.448, 95% confidence interval 0.311-0.643; p=0.000). No statistical heterogeneity was found (I^2=37.02%; p=0.16). Figure 3 is a forest plot for BL. No significant difference in the incidence of BL was found between the two groups of patients (Mantel-Haenszel odds ratio 1.27, 95% confidence interval 0.821-1.966; p=0.283). No statistical heterogeneity was found (I^2=44.65%; p=0.124).

DISCUSSION

The methods of bile duct reconstruction in adult LDLT are mainly DDA and HJ. DDA was adopted in around 70% of the LDLTs in this review. Criteria for selection of bile duct reconstruction method were not stated clearly in most of the papers, and the techniques of bile duct reconstruction varied considerably. The overall rates of BAS and BL were 20.2% and 9.2% respectively. In the comparison of DDA and HJ using pooled data, the former was found to be associated with a bigger chance of BAS but not BL.

It seems that there is a major paradigm shift from HJ to DDA due to the latter's advantages as mentioned in the Introduction. However, the overall impression given by the review is that a good level of evidence supporting the use of a particular bile duct reconstruction method is lacking and thus there is a lack of consensus in the transplant community. This systematic review and meta-analysis includes no randomised controlled trial or prospective study; all the reported studies are retrospective ones. As such, its power is

limited. In addition, publication bias is inevitable in reviews, as only positive papers or papers reporting substantial differences get published. Hence, the results of this meta-analysis require validation by a properly designed and conducted study.

There is an urgent need for a high-power large-volume randomised controlled trial to compare the two bile duct reconstruction methods. On the other hand, whether advantages of DDA over HJ are cancelled out by a bigger chance of biliary complication that DDA entails requires confirmation by a risk-and-benefit-ratio analysis. At our centre, most technical problems (venous outflow, graft size limitation, management of small-for-size syndrome, etc.) have been overcome and complications caused by such problems have decreased over the years. Regrettably, biliary complications are still the major source of morbidities, and results have not further improved. This is why this systematic review and meta-analysis was conducted. The study's indefinite conclusion reflects that trials of adequate quality are urgently needed. The "Achilles' heel" of liver transplantation should be combated by liver transplant surgeons with the backup of a good level of evidence in modern medicine.

At present, our centre is carrying out a randomised controlled trial to determine whether DDA or HJ is the preferable bile duct reconstruction method in right-lobe LDLT by comparing their operative outcomes. It is hoped that the results of the trial will set a milestone in the research of the subject.

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Table 1. Summary of data from the six reference studies

Study	No. of patients	Age (years)	Male : Female	Operation time (minutes)	Biliary complication	BAS	BL
Yi et al. (2005) (16)	74	DDA: 47.7 ± 8.4 HJ: 46.7 ± 10.1	DDA: 47 : 9 HJ: 13 : 5	DDA: 551.6 ± 104.2 HJ: 631.3 ± 149.4	24 (32.4%)	14 (18.9%)	10 (13.5%)
Marubashi et al. (2009) (18)	83	DDA: 50.7 ± 11.3 HJ: 44.2 ± 14.7	DDA: 36 : 25 HJ: 10 : 12	-	7 (8.4%)	6 (7.2%)	1 (1.2%)
Kasahara et al. (2006) (19)	321	DDA: 48.8 ± 11.3 HJ: 35.2 ± 13.5	164 : 157	DDA: 693 ± 173 HJ: 789 ± 192	77 (24.0%)	60 (18.7%)	27 (8.4%)
Hwang et al. (2006) (8)	259	48 ± 7	206 : 53	-	50 (19.3%)	42 (16.2%)	12 (4.6%)
Seo et al. (2009) (21)	239	49 ± 8.8	180 : 59	-	73 (30.5%)	68 (28.5%)	15 (6.3%)
Kyoden et al. (2010) (22)	310	With bile leak: 51 (19 - 64) No bile leak: 51 (18 - 67)	70 : 140 With bile leak: 27 : 26 No bile leak: 143 : 114	With bile leak: 900 (675 - 1212) No bile leak: 898 (640 - 2405)	111 (35.8%)	70 (22.6%)	53 (17.1%)

BAS, biliary anastomotic stricture; BL, biliary leakage; DDA, duct-to-duct anastomosis; HJ: hepaticojejunostomy

Table 2. Pooled-data analysis of biliary complications in the six studies

	DDA	**HJ**	**P**
Biliary anastomotic stricture			**<0.001**
Yes	217 (23.9%)	42 (11.5%)	
No	692 (76.1%)	323 (88.5%)	
Biliary leakage†			0.104
Yes	65 (9.4%)	36 (10.5%)	
No	627 (90.6%)	307 (89.5%)	
Biliary complication†			**0.001**
Yes	219 (31.6%)	74 (21.6%)	
No	473 (68.4%)	269 (78.4%)	

DDA, duct-to-duct anastomosis; HJ, hepaticojejunostomy

† The study by Seo et al. was excluded.

Figure Legends

Figure 1. The search process and the numbers of papers excluded with reasons for exclusion

Figure 2. Forest plot for biliary anastomotic stricture in the six reference studies (BAS, biliary anastomotic stricture; MH, Mantel-Haenszel; CI, confidence interval; HJ, hepaticojejunostomy; DDA, duct-to-duct anastomosis)

Figure 3. Forest plot for bile leakage in the five reference studies (study by Seo et al. was excluded) (MH, Mantel-Haenszel; CI, confidence interval; HJ, hepaticojejunostomy; DDA, duct-to-duct anastomosis)