Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

ORIGINAL ARTICLE
January-February, Vol. 15 No. 1, 2016: 41-46

Risk factors for and management of ischemic-type biliary lesions following orthotopic liver transplantation: A single center experience

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ABSTRACT

Introduction. Biliary complications can cause morbidity, graft loss, and mortality after liver transplantation. The most troublesome biliary complications are ischemic-type biliary lesions (ITBL), which occur since transplants can now be performed after the donor has undergone circulatory death. The exact origin of this type of biliary complication remains unknown. **Material and methods.** A total of 528 patients were retrospectively analyzed following liver transplantation after excluding 30 patients with primary sclerosing cholangitis and those lost to follow-up from January 2007 to January 2014. The incidence of and risk factors for ITBL were evaluated. **Results.** Cold ischemia time (CIT) (P = 0.042) and warm ischemia time (WIT) (P = 0.006) were found to be independent risk factors for the development of ITBL. Use of the cytochrome P450 (CYP) 3A5 genotype assay to guide individualization of immunosuppressive medications resulted in significantly fewer ITBL (P = 0.027. Autoimmune hepatitis might be a risk factor for ITBL, as determined using univariate analysis (P = 0.047). **Conclusions.** Efforts should be taken to minimize risk factors associated with ITBL, such as CIT and WIT. The CYP3A5 genotype assay should be used to guide selection of immunosuppressive therapy in an effort to reduce the occurrence of ITBL.

Key words. Biliary complications. Nonanastomotic strictures. CyP3A5 assay.

INTRODUCTION

Biliary complications have long been recognized as a major source of morbidity and mortality following orthotopic liver transplantation (OLT),[1-3] and have increased with the rising number of organ donations after circulatory death.[4,5] Biliary leaks and strictures are the most common biliary complications. Strictures can be classified as anastomotic or nonanastomotic-depending upon their location. Anastomotic strictures can frequently be successfully treated endoscopically, while nonanastomotic intrahepatic strictures represent a major therapeutic problem. Ischemic-type biliary lesions (ITBLs) are characterized by intrahepatic strictures and dilatations in the absence of other conditions, such as hepatic artery stenosis or thrombosis, portal thrombosis, chronic ductopenic rejection, and primary sclerosing cholangitis.[6] The aims of this retrospective, single-center study analyzing 7 years of OLT experience were to explore possible risk factors for development of ITBL and to establish strategies for its treatment or prevention

MATERIAL AND METHODS

A total of 558 consecutive OLTs from January 2007 to January 2014-were reviewed. All OLTs were carried out at the transplant center of Beijing You-An Hospital affiliated with the Capital Medical University in China. All patients were reviewed and re-examined monthly for the first six months after OLT and every 2-3 months afterwards in a

Manuscript received: February 21, 2014. **Manuscript accepted:** April 20, 2015.

DOI:.10.5604/16652681.1184204

standardized follow-up program. A total of 19 patients were lost to follow-up and the patient follow-up performance was 97.3%. The following criteria were used to diagnose ITBL:

- Postoperative jaundice, usually occurring 3-6 months after transplantation.
- Destruction of non-anastomotic parts of the biliary tree including segmental stenosis and expansion of bile ducts, filling defects, biliary sludge, biliary casts, or bile duct damage, all confirmed by magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cholangiography, or other imaging studies.
- Graft rejection, drug toxicity, and primary disease recurrence were ruled out by liver biopsies; and
- Hepatic artery stenosis or thrombosis, portal thrombosis, ABO-incompatibility, biliary anastomotic stricture, or other reasons for biliary destruction were ruled out. We also intentionally excluded 11 patients that were transplanted for primary sclerosing cholangitis (PSC). Although PSC patients can develop ITBL, there is no diagnostic tool to differentiate between ITBL and PSC recurrence. A final total of 528 OLT patients-were enrolled in this study.

The following clinical variables were analyzed as possible risk factors for ITBL: gender, age, etiology, preoperative model of end-stage liver disease (MELD) score, Child-Pugh score, cold ischemia time (CIT-), and warm ischemia time (WIT). Since most organs have been harvested by our own team-since 2004, we did not analyze WIT during organ harvesting and before cold preservation. We did analyze WIT-during graft implantation and before complete reperfusion-. Based on our clinical experience, underlying rejection or insufficient immunosuppression might cause biliary strictures. Hepatic and intestinal cytochrome P450_(CYP)3A enzymes are the major enzymes that metabolize tacrolimus.[7,8] Carriers of the *CYP3A5 rs776746 GG* genotype metabolize tacrolimus slowly and have a high concentration/dose (C/D) ratio-, while carriers of the *AG* and *AA* genotypes rapidly metabolize tacrolimus and have lower C/D ratios.[9-11] We examined the *CYP3A5* genotype in both OLT recipients and donors from 2010. A higher dose of tacrolimus or an alternate treatment of cyclosporine A was given when patients were found to have *AG* and *AA* genotypes compared to those with GG genotypes and tacrolimus blood concentrations and side effects-were monitored.

All statistical calculations were performed with the SPSS statistical software package (version 16.0; SPSS, Chicago, IL, USA). Descriptive statistics were used to summarize the patient characteristics. Cross-tabulation, the χ^2 test, and Fisher's exact test were performed for independent variables. Variables found to be significant in the univariate analysis were then analyzed by stepwise logistic regression analysis (multivariate analysis) to identify independent factors associated with ITBL. P-values < 0.05 were considered-statistically significant.

This study was approved by the Ethics Committee of Beijing You-An Hospital, and informed written consent was obtained before the patients received treatment according to the Declaration of Helsinki and its amendments.

RESULTS

The overall incidence of ITBL was 7.58% (40/528). There were no significant differences in age or gender between the patients with and without ITBL. MELD scores, Child-Pugh scores, and severe hepatitis were not risk factors for the development of ITBL. Univariate analysis indicated that CIT (692-± 144 *vs.* 624 ± 205 min; P = 0.042) and WIT (73.8-± 35.4 *vs.* 57.1 ± 36.0 min; P = 0.006) significantly associated with ITBL (Table 1). Multivariate logistic regression analysis confirmed that longer CIT (odds ratio [OR], 1.002; 95% confidence interval [CI], 1.000-1.003; P = 0.045) and longer WIT (OR, 1.008; 95% CI, 1.00-1.015; P = 0.026) were independent risk factors for ITBL (Table 2). Patients with autoimmune hepatitis (AIH) had a higher risk of developing ITBL in univariate analysis (P = 0.047) (Table 1) but AIH was not an independent risk factor for ITBL in multivariate analysis (P = 0.053) (Table 2). ITBL occurrence significantly decreased in 2010 based on individualized strategies for immunosuppressive therapy (Table 3). Once the ITBLs were defined, strictures were treated via endoscopy or percutaneous dilatations and stenting. Patients received sirolimus to maintain a blood concentration of 4-8 ng/mL alone or combined with immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisolone. Drug dosage and administration were adjusted according to blood concentration, liver function indices, and clinical symptoms. Retransplantation occurred in 3 cases (7.5 %). The overall mortality rate was 25% (10/40). Patients with ITBL were treated successfully.

DISCUSSION

Liver transplantation is currently a standard treatment for patients with end-stage liver disease. Multiple improvements in patient selection and perioperative management, as well as refinement in surgical technique, have contributed to the modern success of OLT. Unfortunately, biliary complications still reduce patient outcome following OLT.[12] There has recently been an increase in

liver donations after cardiac death in order to expand the organ donor pool. ITBL occurrence has also increased in these cases,[13-,14] reducing the success of liver transplantation. Although several risk factors for ITBL have been recently identified, the cause of ITBL cannot often be identified in an individual patient. The reported incidence of ITBL differs greatly between studies, ranging from 1.4 to 26-%.[6,15-17] This wide range is probably due to the use of different definitions and diagnostic features. In this study, ITBL was diagnosed only if all other known causes for biliary complications were ruled out. There was a relatively low occurrence of ITBL (7.58%) in the 528 OLT patients included in our study and that was after exclusion of patients transplanted for PSC. However, even well trained pathologists have difficulty differentiating between chronic rejection, recurrence of PSC, and ITBL,[18-20] so it is possible that some diagnostic bias remains in our study.

Four statistically significant risk factors for ITBL were identified in our study: CIT, WIT, AIH, and individualized immunosuppressive therapy. Only CIT and WIT remained statistically significant–in multivariate analysis. CIT has been described in many previous studies as a relevant risk factor for ITBL. AIH was previously reported to be a risk factor for ITBL[21] but was not a strong risk factor in our study.

The risk for ITBL-was significantly increased when grafts were preserved for more than 11-13h.[17,-21-23] In our study, the mean CITs for patients with and without ITBL were 692 min (11.5 h) *vs.* 624 min (10.4 h). Many centers try to keep the CIT below 10 h, but even then Guichelaar has shown that the cold storage duration is still a risk factor for ITBL.[21] The strong positive correlation between CIT and ITBL can be explained by either direct ischemic injury of the biliary epithelium or reperfusion injury. It has been previously shown that the duration of CIT correlates with the magnitude of ischemia/reperfusion injury.[24,25] Damage to the peribiliary arterioles could lead to ischemic damage to the biliary epithelium. Researchers have therefore recently begun to focus on graft preservation by normothermic perfusion with oxygenated blood in cases of organ donation after cardiac death.[26,27] This may be one approach to avoid ischemia/reperfusion injury.

WIT, in this study, is considered the period of graft implantation before complete reperfusion. Bile ducts are solely dependent on the hepatic artery for their blood supply. During graft revascularization, the most common technique is initial reperfusion via the portal vein with subsequent reconstruction and reperfusion of the hepatic artery. Bile ducts are exposed to warm ischemia during reperfusion via the portal vein alone, which is thought to increase damage of the biliary epithelium. Reducing WIT to reduce the incidence of ITBL depends on technical improvement.

Studies have indicated that patients transplanted for autoimmune liver disease have a higher incidence of ITBL.[28,29] Since there is no diagnostic tool to differentiate between ITBL and PCS recurrence, we excluded patients with PSC. AIH was a risk factor for ITBL in univariate analysis (P = 0.047), but was not significant in multivariate analysis. More data about AIH would be needed to confirm association of AIH with ITBL. Several studies have provided evidence for an immunological component in the pathogenesis of ITBL.[17,21,30,31] The underlying (auto)

Table 1. Univariate analysis between patients with and without ischemic-type biliary lesions (ITBLs).

Variable	Patients with ITBL n = 40	Patients without ITBL n = 488	P value
Recipient age (y)	47.3 ± 9.5	49.0 ± 10.4	0.306
Recipient sex (M/F)	28/12	389/99	0.147
MELD score (mean ± SD)	18.4 ± 9.5	17.3 ± 10.5	0.509
Child-Pugh score (mean ± SD)	8.8 ± 2.7	8.8 ± 2.8	0.964
Serious hepatitis (%)	12.5	7.8	0.295
Autoimmune hepatitis (%)	15	6.6	0.047
Cold ischemia time (min)	692 ± 144	624 ± 205	0.042
Warm ischemia time (min)	73.8 ± 35.4	57.1 ± 36.0	0.006

Table 2. Multivariate analysis of prognostic factors associated with ischemic-type.

Variable	Odds ratio	95% Confidence interval	P value
Cold ischemia time (min)	1.002	1.000-1.003	0.045
Warm ischemia time (min)	1.008	1.001-1.015	0.026
Autoimmune hepatitis	2.651	0.987-6.645	0.053

Table 3. Incident of ischemic-type biliary lesions (ITBLs) with and without individualized clinical application of immunosuppressive agents based on the *CYP3A5* genotype assay.

Variable	Patients with ITBL	Patients without ITBL	P value
Patients without individualized therapy	21	171	0.027
Patients with individualized therapy	19	317	

immune component could explain the relation between autoimmune liver disease and ITBL.

Chronic rejection has also been implicated in causing biliary strictures.[32-34] However, it is difficult to establish the diagnosis of underlying/early chronic rejection. Tacrolimus is the first-line immunosuppressant after organ transplantation, reducing rejection and improving graft and recipient survival. However, there is a narrow therapeutic window, and large individual differences in metabolism.[35-37] Some patients show insufficient therapeutic effects or serious side effects using "standard" doses of tacrolimus in our experience. Genetic factors such as polymorphisms can influence drug metabolism.[36] We speculate that OLT patients could benefit from individualized therapeutic strategies based on pharmacogenomic research on tacrolimus. Since hepatic and intestinal CYPA3 enzymes affect the pharmacokinetics of tacrolimus, we examined the CYP3A genotype in both recipients and donors from 2010. In our study, individualized tacrolimus therapy based on pharmacogenomics reduced the incidence of ITBL ($P = 0.027$). This finding strengthens the hypothesis that ITBL has an underlying (auto) immune component.

CONCLUSION

ITBL negatively impacts long-term OLT recipient and graft survival. Although the exact pathomechanisms that lead to ITBL remain unclear, our study reinforced that CIT and WIT are risk factors for ITBL. Sufficient preoperative preparation, a suitable operation scheme, and technical improvements on the procedure should be done to minimize these risk factors. Immunopathological damage could underlie ITBL. Designing individualized immunosuppressive therapy based on the *CYP3A5* genotype assay could reduce the occurrence of ITBL, increase recipient and graft survival, and improve patient outcome.

ABBREVIATIONS

- **AIH:** autoimmune hepatitis.
- **CIT:** cold ischemia time.
- **CYP:** cytochrome P450.
- **DCD:** donation after circulatory death.
- **ERCP:** endoscopic retrograde cholangiopancreatography.
- **ITBL:** ischemic-type biliary lesions.
- **MELD:** Model of End-Stage Liver Disease.
- **MRCP:** magnetic resonance cholangiopancreatography.
- **NAS:** nonanastomotic intrahepatic strictures.
- **OLT:** orthotopic liver transplantation.
- **PSC:** primary sclerosing cholangitis.
- **WIT:** warm ischemia time.

ACKNOWLEDGMENTS

This study was supported by Beijing Municipal Commission of Education Fund (Grant No. KM201110025026), Projects of State Commission of Science Technology of China (Grant No. 2012BAI06B01), Capital Development Fund of Medicine (Grant No. 2005-2034), the Capital Health Development Special Funds(Grant No 2011-2018-03), Beijing Municipal Health Bureau(Grant No. 2011-2-18) and Organ Transplantation Research Fund from the Ministry of Health(Grant No. RHECC08-2012-08).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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