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Original Article

The Course of Endoscopic Treatment Success in Biliary Complications After Living Donor Liver Transplantation

Canlı Donörden Karaciğer Nakli Sonrası Biliyer Komplikasyonlarında Endoskopik Tedavinin Başarısının Seyri

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ABSTRACT

Objective: Our aim was to present the results of endoscopic retrograde cholangiopancreatography (ERCP) after living donor liver transplantation (LDLT) between February 2015 and June 2021.

Methods: Clinical data included LDLT indications, time to perform ERCP after LDLT, number of ERCP procedures, indications for ERCP, and all treatment outcomes, including ERCP, percutaneous, and surgical interventions. We compared the obtained data with our previous study published by our team in 2018, which included 446 patients who underwent ERCP for biliary complications after LDLT between 2005 and 2015.

Results: We performed ERCP in 283 of 1506 patients with LDLT who underwent duct-to-duct anastomosis during transplantation and then developed biliary complications. Our endoscopic success rates were 60.9% and 71.0% in the previous and present studies, respectively.

Conclusions: Our findings suggest that the success rate of endoscopic treatment of biliary complications in patients with LDLT increases in correlation with the increasing experience of clinicians treating these patients.

Keywords: ERCP, living donor liver transplantation, biliary strictures, bile leakage

ÖZ

Amaç: Şubat 2015 ile Haziran 2021 tarihleri arasında canlı donör karaciğer transplantasyonu (LDLT) sonrası endoskopik retrograd kolanjiyopankreatografi (ERCP) sonuçlarımızı sunmayı amaçladık.

Yöntemler: Klinik veriler hastaların demografik özelliklerini; LDLT endikasyonları; LDLT sonrası ERCP yapma zamanı; ERCP prosedürlerinin sayısı; ERCP için endikasyonlar; ve ERCP, perkütanöz ve cerrahi müdahaleler dahil tüm tedavi sonuçlarını içeriyordu. Elde edilen verileri, ekibimizin 2018 yılında yayınladığı ve 2005-2015 yılları arasında LDLT sonrası biliyer komplikasyonları nedeniyle ERCP uygulanan 446 hastayı içeren önceki çalışmamızla karşılaştırdık.

Bulgular: Transplantasyon sırasında duct-to duct anastomoz yapılan ve sonrasında biliyer komplikasyon gelişen LDLT'li 1506 hastanın 283'üne ERCP uyguladık. Önceki ve şimdiki çalışmada endoskopik başarı oranımız sırasıyla %60,9 ve %71,0 idi.

Sonuçlar: Bulgularımız, LDLT hastalarında biliyer komplikasyonlarının endoskopik tedavisinin başarı oranının, bu hastaları tedavi eden klinisyenlerin artan deneyimiyle korele olarak arttığını göstermektedir.

Anahtar kelimeler: Canlı donör karaciğer transplantasyonu, ERCP, biliyer darlık, safra kaçağı

INTRODUCTION

Liver transplantation (LT) is a life-saving treatment for patients with end-stage liver disease and acute liver failure. Living donor liver transplantation (LDLT) has emerged as a standard procedure, especially in developing Eastern countries, to resolve the inadequacy of cadaveric organ donation and ensure the timely supply of organs[1]. Currently, both the European Liver Transplant Registry and the Scientific Registry of Transplant Recipients report a 1-year survival rate of approximately 90% of liver transplant recipients[2].

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Biliary complications (BCs) are the most common complications after LT. Despite advances in surgical techniques and medical treatments, BCs remain an important cause of morbidity in patients who undergo LT. Endoscopic, percutaneous, and surgical procedures are used to treat BCs; however, these procedures are time-consuming. In general, the frequency of BCs after LT varies between 5% and 20%. Most BCs occur within the first 3 months after LT; occasionally, BCs can occur several years after transplantation[3].

BCs after LDLT contain bile leakage, biliary strictures, and stone formation. Although BCs do not have a significant effect on patient and graft survival, they could lead to significant morbidity because of long treatment processes[4]. Therefore, proper management of these complications is crucial for patient well-being. The first treatment for patients with BC after LDLT is endoscopic retrograde cholangiopancreatography (ERCP)[5]. Percutaneous transhepatic biliary intervention (PTBI) is performed in patients with Roux-en-Y hepaticojejunostomy, a type of biliodigestive anastomosis that technically complicates ERCP, and in patients with failed ERCP. Surgery is the last treatment for patients with failed endoscopic or percutaneous treatments.

Our center has the highest volume of LT cases in Turkey (200-250 LDLT per year). We previously reported the results of patients who underwent ERCP for BC after LDLT between February 2005 and January 2015[6]. In this study, we present our last ERCP results after LDLT between February 2015 and June 2021.

MATERIALS and METHODS

In the present study, we retrospectively analyzed the data of patients who underwent ERCP due to BCs after LDLT in the Inonu University Liver Transplant Unit (Malatya-Turkey) between February 2015 and June 2021. The Inonu University Health Sciences Non-invasive Clinical Research Ethics Committee approved our study (decision no: 2022/3456, date: 26.04.2022).

Table 1 included patient demographic data.

Before ERCP, each patient was evaluated on the basis of their clinical data and imaging findings, including percutaneous cholangiography or magnetic resonance imaging, in a multidisciplinary meeting that included transplant surgeons, radiologists, and gastroenterologists. Biliary strictures were suspected in cases of elevation in liver function test parameters or in the presence of cholangitis. The diagnosis was made by computed tomography and MR cholangiopancreatography or percutaneous cholangiography. We preferred ERCP as the first treatment in patients with duct-to-duct anastomosis if there were signs of biliary strictures. Percutaneous catheter cholangiography was performed for clinical indications and was routinely performed approximately 90 days after LT, immediately before catheter removal. We applied the diluted contrast reagent iopromide (Ultravist; Shering, Berlin, Germany) to confirm the presence of BCs during percutaneous cholangiography.

Experienced gastroenterologists performed ERCP. They used Olympus duodenoscopes (Olympus Optical Co., Ltd., TJF-160, Tokyo, Japan). We used endoscopic sphincterotomy (EST) on the patient during ERCP if BCs were detected by laboratory and imaging methods. If a biliary stricture was detected on cholangiography performed with a contrast medium, we attempted to enter the intrahepatic bile ducts by passing a 0.025- or 0.035-inch "straight" or "J-Form" guidewire (Micro-Tech Co., Ltd.) through the stricture. We used a sphincterotomy, an ERCP catheter, and stone balloon catheters to pass through the stricture. After the stricture was passed through with the guidewire, stricture dilatation was performed with a bougie (7 and 10 French, Winston Salem, Wilson-Cook Medical GI Endoscopy, NC, USA) and/or a balloon catheter (4, 6, or 8 mm, Boston Scientific, Hurricane RX; MA, USA). Next, biliary stents (Micro-Tech Co., Ltd, 7-10 French, 9-18 cm long) were placed proximal to the stricture. Based on the ESGE guidelines, stent revision was performed with the ERCP procedure conducted again every 3-4 months for a 12-month period in patients in whom the procedure was successful. At the end of 12 months, stenting was

Table 1. Demographic data of the study patients.

Parameter	Value
Age, mean ± SD	47.36±13.33
Gender, n (%)	
Male	198 (70%)
Female	85 (30%)
Mean procedure number, mean ± SD	7.00±4.08
Time to perform first ERCP, mean ± SD (months)	3.50±4.11
Recurrence time, mean ± SD (months)	5.27±12.82
Etiology, n (%)	
HBV	78 (27.6)
HCV	15 (5.3)
Autoimmune hepatitis	11 (3.9)
Budd Chiari syndrome	16 (5.7)
Cryptogenic	64 (22.6)
Others	99 (34.9)

SD: Standard deviation, HBV: Hepatitis B virus, HCV: Hepatitis C virus, ERCP: Endoscopic retrograde cholangiopancreatography

Table 2. PTBI and surgical treatment rates according to ERCP findings.

ERCP findings	ERCP success		PTBI		Surgery		Total
	No	Yes	No	Yes	No	Yes	
Stricture ± stone	51 (23.6%)	159 (76.4%)	159 (76.4%)	49 (23.6%)	206 (99%)	2 (1%)	208 (73.5%)
Leak	6 (42.9%)	8 (57.1%)	8 (57.1%)	6 (42.9%)	13 (92.8%)	1 (7.2%)	14 (4.9%)
Stricture + leak	15 (38.5%)	24 (61.5%)	24 (61.5%)	15 (31.5%)	35 (89.7%)	4 (10.3%)	39 (13.8%)
Single stone	2 (66.7%)	1 (33.3%)	1 (33.3%)	2 (66.7%)	3 (100%)	0	3 (1.1%)
Normal	1 (12.5%)	7 (87.5%)	7 (87.5%)	1 (12.5%)	8 (100%)	0	8 (2.8%)
Fistula	1 (50%)	1 (50%)	1 (50%)	1 (50%)	2 (100%)	0	2 (0.8%)
Fail to pass due to duodenal ulcer	3 (75%)	1 (25%)*	1 (25%)	4 (75%)	4 (100%)	0	4 (1.4)
No cannulation	5 (100%)	0	0	5 (100%)	5 (100%)	0	5 (1.8%)
Total	72 (39%)	201 (71%)	201 (71%)	82 (29%)	276 (97.5)	7 (2.5)	283 (100%)

*In one patient, the ulcer was healed with medical treatment, and the stricture was then treated with ERCP. PTBI: Percutaneous transhepatic biliary intervention, ERCP: Endoscopic retrograde cholangiopancreatography

continued in patients whose strictures remained. Our goal was to improve the stricture immediately and to resolve it without a stent. Therefore, we attempted to increase the number and caliber of stents in each session. During ERCP sessions, anastomotic strictures were evaluated in each session, and if the stricture was found to be resolved, we took biliary stents and followed up without a stent. If the stricture persisted, we re-dilated and re-stented.

In patients with duct-to-duct anastomosis in whom bile leakage was detected on cholangiogram performed by placing a T-tube catheter in the bile duct by surgeons during the transplant, we chose ERCP as the first treatment. If bile leakage was detected during ERCP, we placed bile stents after EST to stop the leakage. If stones were detected during ERCP or imaging, they were removed with a basket catheter or balloon. If ERCP failed (failure to pass the stricture or permanent BCs), our multidisciplinary team chose to perform PTBI as the second treatment approach and surgical treatment as the third treatment approach. After successful percutaneous drainage with PTBI and stabilization of the patient, we continued stent revisions with ERCP. In our study, patients who did not undergo surgery or PTBI due to BCs at any time during the initial post-ERCP follow-up were considered to have successfully undergone ERCP.

Recurrence of biliary stricture was defined as the need for re-endoscopic treatment in patients scheduled to undergo follow-up without stent placement in ERCs performed after 12 months of stenting.

Statistical Analysis

Data were entered and statistically analyzed using SPSS (SPSS Inc., Chicago, IL, USA). We used chi-square test was used for comparisons, and p-values of <0.05 were considered to be statistically significant.

RESULTS

We performed ERCP in 283 of 1506 patients with LDLT who underwent duct-to-duct anastomosis during transplantation and then developed BCs. Of the 283 patients, 198 (70%) were male and 85 (30%) were female. Hepatitis B [78 (27.6%) patients] was the most common etiology. Table 1 shows the patient demographic data in detail. Anastomotic stricture [208 (73.5%) patients] was the most common BC. The coexistence of leakage and biliary stricture was observed in 39 (13.8%) patients. We could not cannulate the bile duct in five (1.8%) patients, and we could not pass into the duodenum in four (1.4%) patients because of ulcers in the bulb. In one patient, the ulcer was healed with medical treatment, and the structure was then treated with ERCP. The findings of ERCP are shown in Table 2 in detail.

BCs were successfully treated with endoscopic therapy in 71% of the patients. Although the highest success rate was 76.4% in patients with biliary strictures, the success rate was only 57.1% in those with bile leakage. Of all patients, 97.5% were successfully treated with endoscopic therapy and PTBI. Only 2.5% of all patients underwent surgical treatment.

Recurrence was detected in 53 (18.7%) patients who were followed up. At the end of the study, 185 (65.4%) patients were followed up without a stent. The remaining 98 (34.6%) patients were still undergoing endoscopic treatment (stent revision).

We compared the success rate of ERCP in our current study with that in our previous study, which included 446

LDLT patients who underwent ERCP between February 2005 and January 2015. Although our success rate was 60.9% in the previous study, it improved to 71.0% in our current study ($p<0.01$)[5].

Cholangitis (n=15) (5.3%) and moderate elevation of amylase level (n=38) (13.4%) were the most common complications after ERCP. The incidence of severe pancreatitis (n=3) (1.06%) and bleeding from the EST area (n=2) (0.70%) was extremely rare. No deaths occurred because of complications.

DISCUSSION

In this study, 71.0% of patients who underwent ERCP for BCs after LDLT were successfully treated with endoscopic treatments. Of all patients, 97.5% were successfully treated with endoscopic and percutaneous interventions. Surgical treatment was required in the remaining 2.5% of patients.

BCs are more common after LDLT than after deceased donor liver transplantation (DDLT) because of the small size of the bile ducts and the frequent need for two or more anastomoses from the donor right liver lobe[7]. The success rates of ERCP in BCs after LDLT are lower than those after DDLT. This lower success rate for LDLT patients than for DDLT patients can be attributed to multiple, small-bore anastomoses, twisted structures, and peripheral locations, which possibly result from anastomotic fibrosis and hypertrophy of the transplanted liver[8]. The most common BC after LDLT is biliary strictures[9]. In previous studies, the success rates of endoscopic treatment for biliary strictures after LT were reported to be 68.0-86.4%[10-15]. Park et al.[16] reported a 66.2% success rate of endoscopy in 219 patients with strictures after LDLT. In a study by Tsujino et al.[12] investigating 174 LDLT patients who underwent duct-to-duct anastomosis, ERCP was performed in 17 patients due to biliary stenosis and was successful in 12 (71%)[17]. Hsieh et al.[18] retrospectively examined 110 patients who underwent LDLT and duct-to-duct anastomosis. They achieved endoscopic success in 32 of 38 patients (84%) with anastomotic stricture[18]. In a study conducted with 96 patients with biliary stricture, Sato et al.[19] reported an ERCP success rate of 87.5%. In our present study, the success rate of ERCP was 61.5% in the group of patients with biliary strictures and leakage, whereas it was 76.4% in patients with only strictures. The high success rate in the latter group is consistent with that reported in the literature. Thus, our results suggest that ERCP is an effective treatment method in patients with strictures, and endoscopic treatments should be preferred as the first treatment choice in patients with strictures after LDLT.

Although small liquid collections due to bile leakage may resolve spontaneously after LT, larger liquid collections may cause a mass effect or become secondarily infected[20]. Non-ischemic bile leaks usually respond to non-surgical diversion of bile flow, such as unclamping the T-tube, EST, or PTBI. Often, simple drainage from the tube opening can be therapeutic, thus preventing any invasive treatment. For other cases, endoscopic therapy should be the first-line treatment. In the case of minor bile leakage, EST with ERCP alone may be curative[21]; however, stent placement may be required for major bile leakage. Bile leaks occur in the range of 2-25% after transplantation. The majority of bile leaks occur 1 day to 6 months after transplantation. ERCP is highly effective in both diagnosing and treating bile leakage and usually requires an average of two ERCP sessions. Plastic stent treatment with ERCP resolved early bile leaks in 90-95% of cases[17]. In a previous study, these patients were followed up with a stent for 2-3 months, and the success rate was approximately 95%[22]. In our present study, although our endoscopic success rate was 57.1% in only 14 patients with leakage, it was 61.5% in 39 patients with leak + stricture. Endoscopic treatment outcomes in patients with post-LDLT leaks are highly variable. Tarantino et al.[23] reported a very low success rate of 22.2% in 18 patients; however, other studies have reported very high success rates of 82% and 100%. Yazumi et al.[11] reported a 50% success rate in 16 patients. In a series of 13 patients, Lee et al.[24] reported a success rate of 69.2% and Wadhawan et al.[14] reported 82% success (14/17 patients). In our present study, although our endoscopic success rate for bile leakage appears to be lower than that in patients with only strictures, we can say that this endoscopic success rate is a reasonable rate when compared with those reported in the literature.

In a study by Han et al.[25], the average time to diagnosis of biliary strictures after LDLT was 4.2 months, whereas in our study it was approximately 3.5 months. These results suggest that BCs after LDLT are more common in the first 6 months postoperatively.

Cannulation problems (5/283, 1.8%) were the main causes of endoscopic failure in our study, failure to pass the pylorus due to duodenal ulcer (4/283, 1.4%), and failure to pass the stricture despite dilatation and stent placement or persistent biliary problems (89/283, 31.5%) (Table 2). When the biliary issue cannot be resolved with ERCP, the next treatment option is PTBI. Surgical treatment is usually considered as the last option. After successful percutaneous drainage with PTBI, we performed stent revision by ERCP. While the success rate with the combination of endoscopy and PTBI in patients with stricture, leak, and stricture + leak was

91.4%, 85.0%, and 88.3%, respectively, in our previous study, these rates were 99.0%, 92.8%, and 89.7% in our current study, respectively. In all patients, the endoscopy + PTBI success rate was 90.6%, which improved to 97.5% in this study. These results suggest that the success rates of endoscopy + PTBI are increasing, especially in patients with strictures and leaks. An increase in the success rates of endoscopy + PTBI in this patient group will reduce the need for surgical treatment. This situation may also contribute positively to reducing the morbidity and mortality of LDLT patients.

Although our clinic has more than 35 years of experience in ERCP, ERCP in patients with LDLT was initially very difficult for us because of the above reasons. In fact, although our endoscopic success rate was 60.9% in our ERCP results between February 2005 and January 2015[6], our success rate increased to 71.0% in the present study covering the years between February 2015 and June 2021 ($p<0.01$). This finding suggests that as the experience in the endoscopic treatment of BCs after LDLT increases, the success rate increases in parallel.

In the current study, we found that the success rates for both endoscopy and endoscopy + PTBI increased. This result seems to be related to the fact that our center is a high-volume liver transplant center with a multidisciplinary team of interventional gastroenterologists, radiologists, and surgeons who have a rich experience of treating LDLT patients in particular.

CONCLUSION

In conclusion, our findings suggest that the success rate of endoscopic treatment and endoscopy + PTBI treatment for BCs in patients with LDLT increases in correlation with the increasing experience of clinicians treating these patients.

Ethics

Ethics Committee Approval: The Inonu University Health Sciences Non-invasive Clinical Research Ethics Committee approved our study (decision no: 2022/3456, date: 26.04.2022).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: E.A., Y.B., M.A.E., R.K., K.K., Concept: E.A., M.H., Y.F.C., Design: E.A., M.H., Y.B., Data Collection and/or Processing: E.A., M.A.E., I.O., O.S., A.R.C., Analysis and/or Interpretation: E.A., Y.F.C., R.K., Literature Search: E.A., R.K., I.O., O.S., A.R.C., Writing: E.A., M.H.

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

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