

Feasibility of Endoscopic Papillary Large Balloon Dilation in Patients with Difficult Bile Duct Stones without Dilatation of the Lower Part of the Extrahepatic Bile Duct

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Background/Aims: There is no consensus for using endoscopic papillary large balloon dilation (EPLBD) in patients without dilatation of the lower part of the bile duct (DLBD). We evaluated the feasibility and safety of EPLBD for the removal of difficult bile duct stones (diameter ≥ 10 mm) in patients without DLBD. **Methods:** We retrospectively reviewed the records of 209 patients who underwent EPLBD for the removal of bile duct stones from October 2009 to July 2014. Primary outcomes were the clearance rate and additional mechanical lithotripsy. Secondary outcomes were the incidence of complications and recurrence rate. **Results:** Fifty-seven patients had DLBD (27.3%), and 152 did not have DLBD (72.7%). There were no significant differences in the overall success rate or the use of mechanical lithotripsy. Success rate during the first session and procedure time were better in the DLBD than the without-DLBD group (75.7% vs 66.7%, 48.1 \pm 23.0 minutes vs 58.4 \pm 31.7 minutes, respectively). As for complications, there were no significant differences in the incidence of pancreatitis, perforation or bleeding after endoscopic retrograde cholangiopancreatography. The recurrence rate did not differ significantly between the two groups. **Conclusions:** EPLBD is a useful and safe method for common bile duct stone removal in patients without DLBD. (*Gut Liver* 2017;11:149-155)

Key Words: Cholangiopancreatography, endoscopic retrograde; Common bile duct stone

INTRODUCTION

Endoscopic sphincterotomy (EST) combined with mechanical lithotripsy (ML) is a feasible method for the removal of difficult biliary stones. However, we often encounter challenging cases that require multiple procedures and are complicated with post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, perforation, and massive bleeding. Endoscopic papillary balloon dilation (EPBD) was introduced in 1982 to preserve the sphincter function and decrease bleeding caused by EST.¹ In 2004, a Japanese randomized controlled clinical trial of EPBD confirmed the safety and efficacy of this procedure for common bile duct (CBD) stones <14 mm in diameter.² However, some bile duct stones were difficult to remove because of their large size, rectangular shape of the CBD, or anatomical difficulties interfering with endoscopic procedures. In 2003, Ersoz *et al.*³ first reported the usefulness of large balloon dilation (12 to 20-mm diameter) after EST (endoscopic papillary large balloon dilation, EPLBD) for the removal of large bile duct stones. Since then, EPLBD has been used in Japan. Itoi *et al.*⁴ demonstrated the safety and feasibility of EPLBD and extended its application to multiple large stones >13 mm in diameter. Difficult cases have been encountered with large stones and without dilatation of the lower part of the CBD (DLBD). The combination of EST and ML in such cases often requires multiple procedures, whereas EPLBD has been avoided so far because of the high risk of procedure-associated complications.

We hypothesized that the indications of EPLBD could be extended to include the treatment of difficult large stones without DLBD. The aim of this study was to verify the technical feasibility

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ity and safety of EPLBD for the removal of difficult CBD stones in patients without DLBD. We defined difficult stones as diameter ≥ 10 mm.⁵ To this end, we conducted a retrospective cohort study of patients with or without DLBD.

MATERIALS AND METHODS

1. Patients

Between March 2008 and July 2014, 209 patients underwent EPLBD for the removal of bile duct stones at Yokohama City University Hospital and NTT Tokyo Medical Center. Before initial ERCP, CBD stones were identified in all patients by imaging, including abdominal ultrasonography, computed tomography, or magnetic resonance cholangiopancreatography. The study was approved by the Institutional Review Board of our hospital, and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

2. Definition of without DLBD

Without DLBD was defined as a state in which the diameter of the lower part of the extrahepatic bile duct was <10 mm and its length >10 mm as measured by cholangiography. The diameter of the lower part of the bile duct was measured at 10 mm proximal to the opening of the major ampulla, and we measured the length of the bile duct less than 10 mm from the opening of the major papilla.

3. Procedures

ERCP was performed by experienced biliary endoscopists (>200 procedures annually). All procedures were carried out with the patients under moderate sedation with intravenous diazepam or midazolam. ERCP was performed using side-viewing endoscopes (JF-260V or TJF-260V; Olympus Medical Science Corp., Tokyo, Japan). Cannulation was attempted using an ERCP catheter or a pull-type sphincterotome. Cholangiography was performed to confirm the diagnosis of CBD stones after selective cannulation of the CBD. A 0.035-inch guidewire (Jagwire;

Boston Scientific, Boston, MA, USA) was then inserted into the bile duct through the catheter. A large dilating balloon (CRE, Boston Scientific; GIGA, Century Medical, Tokyo, Japan) was introduced into the bile duct along the prepositioned guidewire and positioned to be able to cover all of the length of without DLBD.

The decision to perform EST was made by the endoscopist based on the patient's background. In particular, EST was carried out in patients with high risk of postprocedural pancreatitis, and avoided in patients with large periampullary diverticula. Balloons were gradually inflated until the balloon notches disappeared, and then they were immediately deflated. EPLBD was terminated upon disappearance of the balloon notches, or if the patient complained of pain, to reduce adverse events. If the patients experienced pain before the maximum pressure was reached, we immediately deflated the balloon before the notches disappeared. Therefore, we did not achieve the maximum pressure. The size of the inflated balloon was selected based on the diameter of the CBD or the largest stone. After EPLBD, a basket or retrieval balloon catheter was used to extract the CBD stones (Fig. 1). ML (Xemex Lithotripsy Basket Catheter; Zeon Medical, Tokyo, Japan) was attempted when stones were too difficult to remove. If stone removal was incomplete, a nasobiliary tube or a plastic stent was placed to prevent cholangitis. All patients were observed in the hospital for at least 72 hours after endoscopic treatment.

In patients with surgically altered anatomy, including Billroth II and Roux-en-Y anastomosis, ERCP was performed using a single-balloon enteroscope (SIF-Q260; Olympus Medical Science Corp.). We did not perform EST in patients with reconstructed intestine because of the high risk of bleeding and perforation.

4. Outcome measurements and adverse events

The primary outcomes were the bile duct clearance rate in a single session and the need for additional ML after EPLBD. Although large stones were fragmented during ML, this procedure required more time and resulted in a higher rate of stone

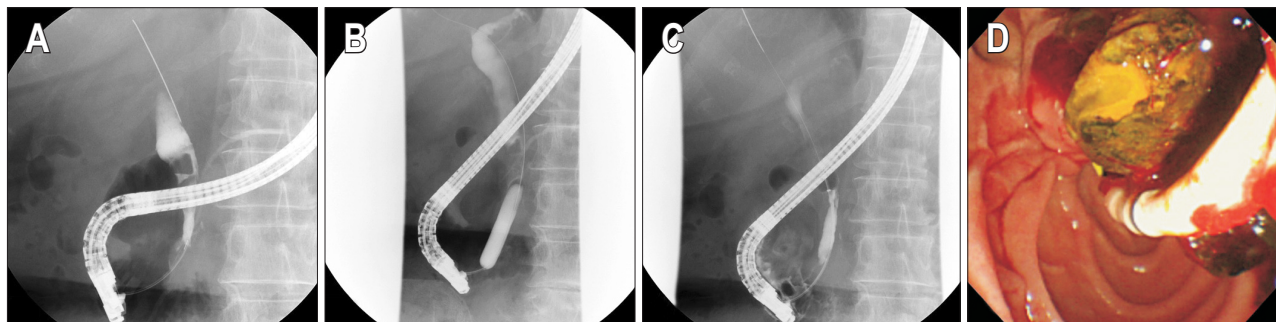


Fig. 1. Endoscopic papillary large balloon dilation (EPLBD) in a patient without dilatation of the lower bile duct. (A) Cholangiography showing multiple movable filling defects and no dilatation of the lower bile duct (5.7 mm). (B) Fluoroscopic view showing disappearance of the balloon waist after gradual inflation with contrast medium. (C) The lower bile duct was dilated (10.3 mm) as the result of EPLBD. (D) Endoscopic view showing a large brown pigment stone.

recurrence. The secondary outcomes were the incidence of post-ERCP complications and the recurrence rate after stone removal. Complications included pancreatitis, bleeding and perforation. Procedure-related complications and their incidence were determined according to the definitions and grading systems suggested by the workshop held by the American Society of Gastrointestinal Endoscopy in 2010.⁶

5. Statistical analysis

Statistical analysis was carried out using Student t-test and the chi-square test. Multivariate analysis was performed using logistic regression analysis. A value of $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using Excel-Toukei 2010 for Windows (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

1. Patient demographics

The demographics of the 209 patients (113 men, 96 women; mean age, 78.5 ± 10.7 years) are presented in Table 1. The patients were divided into groups with and without DLBD. Fifty-seven patients (27.3%) were without DLBD. The mean diameter of the lower part of the bile duct was 8.2 ± 0.9 mm (range, 7 to 9 mm) in the without-DLBD group and 13.3 ± 2.1 mm (range, 10 to 16 mm) in the DLBD group ($p < 0.001$). The greatest diameter of the bile duct was 19.3 ± 4.5 mm (range, 12 to 25 mm) in the

without-DLBD group and 18.5 ± 4.8 mm (range, 12 to 35 mm) in the DLBD group ($p = 0.663$). Billroth II anastomosis had been performed in two patients (3.3%) in the non-DLBD group and in five (3.3%) in the DLBD group ($p = 0.680$). Roux-en-Y anastomosis had been performed in four patients (7.0%) in the without-DLBD group and in five (3.2%) in the DLBD group ($p = 0.424$). The frequency of EST did not differ significantly between the two groups (35.1% vs 44.1%, $p = 0.207$). The mean diameter of the largest stones was 15.2 ± 9.2 mm (range, 10 to 51 mm) in the without-DLBD group and 13.7 ± 4.6 mm (range, 10 to 30 mm) in the DLBD group ($p = 0.165$). The mean size of the inflated balloon during EPLBD was 14.3 ± 2.0 mm (range, 12 to 20 mm) in the without-DLBD group and 14 ± 2.4 mm (range, 12 to 20 mm) in the DLBD group ($p = 0.040$). The follow-up period was 26 ± 19.7 months (range, 12 to 20 months) in the without-DLBD group and 28 ± 20.4 months (range, 1 to 77 months) in the DLBD group.

2. Outcomes

The primary outcomes are shown in Table 2. The stone clearance rate was 100% (57/57) in the without-DLBD group and 98.7% (150/152) in the DLBD group. Additional ML was required in 33.3% (19/57) of the without-DLBD group and 23% (35/152) in the DLBD group ($p = 0.311$). The mean diameter of the lower part of the bile duct after EPLBD was 11 ± 1.5 mm (range, 8 to 13 mm) in the without-DLBD group and 14.0 ± 2.1 mm (range, 10 to 18 mm) in the DLBD group. Table 3 dem-

Table 1. Baseline Characteristics of Patients

Characteristic	Total (n=209)	Without-DLBD group (n= 57)	DLBD group (n=152)	p-value
Mean age, yr	78.5 ± 10.7 (39–95)	78.9 ± 10.5 (39–93)	78.3 ± 12.5 (58–95)	0.697
Sex, male:female	113:96	31:26	70:82	0.283
Billroth II anastomosis	7 (3.3)	2 (3.3)	5 (3.3)	0.680
Roux-en-Y anastomosis	9 (4.3)	4 (7.0)	5 (3.2)	0.424
Large balloon dilation				
With EST	87 (41.6)	20 (35.1)	67 (44.1)	0.207
Without EST	123 (58.9)	38 (66.7)	85 (55.9)	-
CBD stones				
Mean diameter of stone, mm	14.2 ± 6.2 (10–51)	15.2 ± 9.2 (10–51)	13.7 ± 4.6 (10–30)	0.165
No. of stones				
1/2/3/>4	65/26/25/90	19/5/11/22	45/21/14/69	0.947
Greatest diameter of bile duct, mm	18.8 ± 4.7 (12–35)	19.3 ± 4.5 (12–25)	18.5 ± 4.8 (12–35)	0.663
Diameter of lower part of bile duct, mm*	11.3 ± 3.0 (6–18)	8.2 ± 0.9 (7–9)	13.3 ± 2.1 (10–16)	<0.001
Dilating balloon size, mm	14.3 ± 2.0 (12–20)	14.8 ± 1.8 (12–20)	14 ± 2.4 (12–20)	0.400
Bile duct diameter <10 mm from opening of major papilla, mm	-	17.9 ± 4.8 (10–30)	-	-
Follow-up period, mo	27 ± 20.2 (1–77)	26 ± 19.7 (1–72)	28 ± 20.4 (1–77)	0.600

Data are presented as the mean \pm SD (range) or number (%).

Diameter of the lower part of the bile duct measured at 10 mm proximal to the opening of the major papilla.

DLBD, dilatation of the lower part of the bile duct; EST, endoscopic sphincterotomy; CBD, common bile duct.

Table 2. Results of Stone Clearance with EPLBD

Variable	Without-DLBD group (n=57)	DLBD group (n=152)	p-value
Overall stone removal	57 (100)	150 (98.7)	0.942
Complete stone removal in first session	38 (66.7)	117 (75.7)	0.130
Additional mechanical lithotripsy	19 (33.3)	35 (23.0)	0.311
Diameter of lower part of bile duct after EPLBD, mm	11±1.5 (8–13)	14.0±2.1 (10–18)	<0.001
Procedure time, min	58.4±31.7 (13–143)	48.1±23.0 (13–152)	0.010
Reccurence CBD stones	1 (1.8)	7 (4.6)	0.581

Data are presented as the number (%) or mean±SD (range).

Diameter of the lower part of the bile duct measured at 10 mm proximal to the opening of the major ampulla.

EPLBD, endoscopic papillary large balloon dilation; DLBD, dilatation of the lower part of the bile duct; CBD, common bile duct.

Table 3. Factors for Additional Lithotripsy by Univariate and Multivariate Analysis

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
EST	0.966	0.508–1.839	0.917	0.966	0.484–1.929	0.922
Reconstructed intestine (B-II or R-Y)	0.631	0.173–2.309	0.487	0.612	0.154–2.433	0.486
Stone number >4	1.667	0.777–2.768	0.237	1.542	0.838–3.682	0.204
Diameter of largest stone >15 mm	3.273	1.701–6.297	<0.001	3.089	1.593–5.991	0.001
Without DLBD	1.693	0.843–3.398	0.139	1.757	0.838–3.682	0.135

OR, odds ratio; CI, confidence interval; EST, endoscopic sphincterotomy; B-II, Billroth II; R-Y, Roux-en-Y; DLBD, dilatation of lower part of bile duct.

Table 4. Factors for Multiple Sessions by Univariate and Multivariate Analysis

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
EST	1.287	0.701–2.365	0.416	1.512	0.757–3.019	0.241
Stone number >4	2.492	1.345–4.619	0.004	2.984	1.489–5.979	0.002
Diameter of largest stone >15 mm	2.654	1.429–4.928	0.002	1.718	0.852–3.465	0.130
Additional ML	4.788	2.422–9.469	<0.001	3.917	1.876–8.179	<0.001
Without DLBD	1.866	0.977–3.566	0.059	2.396	1.116–5.145	0.025

OR, odds ratio; CI, confidence interval; EST, endoscopic sphincterotomy; ML, mechanical lithotripsy; DLBD, dilatation of lower part of bile duct.

onstrates that absence of DLBD was not an independent risk factor for additional ML as determined by multivariate analysis ($p=0.135$; odds ratio, 1.757; 95% confidence interval, 0.838 to 3.682).

There was no significant difference in the bile duct clearance rate in a single session between the without-DLBD and DLBD groups (100% vs 98.7%, $p=0.942$; 66.7% vs 75.7%, $p=0.130$, respectively). Multiple sessions of ERCP were required in patients with several stones, additional ML and without DLBD (Table 4). Table 4 reveals that without DLBD was a risk factor for multiple sessions of ERCP by multivariate analysis ($p=0.025$; odds ratio, 2.396; 95% confidence interval, 1.116 to 5.145). In addition, the procedure time was significantly longer in the without-DLBD group (58.4±31.7 vs 48.1±23.0, $p=0.010$). The recurrence rates were not significantly different between the without-DLBD and

DLBD groups (1.8% vs 4.6%, $p=0.581$, respectively).

3. Complications

The data on secondary outcomes are shown in Table 5. The rates of post-ERCP pancreatitis (7% vs 3.3%, $p=0.424$), perforation (0% vs 1.3%, $p=0.942$), and bleeding (1.8% vs 0.7%, $p=0.924$) were not significantly different between the without-DLBD and DLBD groups. Similarly, there was no significant difference in the levels of serum amylase after 24 hours (240.8±318.5 [range, 29 to 1,689 IU] in the without-DLBD group and 240.5±315.1 [range, 22 to 2,465 IU] in the DLBD group, $p=0.554$). Although there were six cases of mild and three of moderate pancreatitis, none of the patients developed severe pancreatitis after EPLBD. Two cases of minor perforation in the DLBD group were treated conservatively. Massive bleeding that

Table 5. Comparison of Complications between the Groups

Variable	Non-DLBD group (n=57)	DLBD group (n=152)	p-value
Pancreatitis	4 (7)	5 (3.3)	0.424
Mild	3 (5.3)	3 (2)	0.422
Moderate	1 (1.8)	2 (1.3)	0.678
Perforation	0	2 (1.3)	0.942
Bleeding	1 (1.8)	1 (0.7)	0.924
Major	1 (1.8)	0	0.609
Minor	0	1 (0.7)	0.609
Amylase after 24 hr	240.8±318.5 (29–1689)	240.5±315.1 (22–2465)	0.554

Data are presented as the number (%) or mean±SD (range).
DLBD, dilatation of lower part of bile duct.

occurred in one patient in the without-DLBD group was treated by interventional radiology.

DISCUSSION

This study presents three important clinical observations. First, stone clearance rate in patients without DLBD was 100%, and it was not an independent risk factor for additional ML. Second, EPLBD appeared to be a safe method for CBD stone removal in patients without DLBD. Third, stone recurrence rate was similar in the patients with and without DLBD.

Recently, EPLBD has been performed in patients with large stones (>10 mm) and dilated CBDs (>10 mm). Lower complication rates have been reported for EPLBD compared with EST with a large incision for the removal of difficult bile duct stones.^{3,7-10} However, there is no consensus regarding the diameter of the lower part of the bile duct suitable for EPLBD. We encountered cases with large stones and tapering of the lower part of the CBD, which might make it difficult to extract the stones by EST or EPBD combined with ML. Therefore, we hypothesized that EPLBD could be extended to include such challenging cases.

EPLBD leads to wide opening of the papillary orifice in patients with large stones, thereby facilitating effective extraction of difficult stones.^{11,12} It can also reduce the use of ML and the overall procedure time.^{4,13} However, the shape of the bile duct amenable to this procedure is a matter of debate. We revealed that stone clearance rate in patients without DLBD was 100%, but more time and more sessions were required to complete stone removal than in patients with DLBD. A benefit of EPLBD was the wide opening of the papillary orifice. In this study, we dilated the lower part of the bile duct in the without-DLBD group (8.2±0.9 to 11±1.5 mm). However, the diameter of the lower part of the bile duct after EPLBD in the without-DLBD group was smaller than that of the lower part of the bile duct after EPLBD in the DLBD group (11±1.5 mm vs 14.0±2.1 mm, $p<0.001$). Therefore, we consider that the difference resulted from the number of sessions and the time required. In con-

trast, the rate of additional ML did not differ (33.3% vs 23.0%, $p=0.311$). In this regard, additional ML was required in 80% of patients who underwent EPBD.¹⁴ The diameter of the lower part of the bile duct after EPLBD was extended to >10 mm, which avoided the need for additional ML. Moreover, more time and sessions were required to treat cases without DLBD with EPBD. These shortcomings of EPBD may be overcome with EPLBD. Therefore, EPLBD against without DLBD was a more useful method to remove the difficult stones than EPBD against without DLBD. In addition, lowering the frequency of additional ML is important to prevent recurrent bile duct stones because stone fragments remaining after lithotripsy can act as nuclei for subsequent stone formation. This suggests that EPLBD in patients without DLBD reduced the recurrence rate more than EPBD did. Reducing the recurrence rate lowers hospitalization costs as well as the risk of cholangitis.

Our target of EPLBD was maximum dilation of the bile duct in a safe range. It was most important to safely enforce EPLBD. EPLBD was also acceptable for CBD stone removal in patients without DLBD provided that the complication rate was the same as in the DLBD group. Post-ERCP pancreatitis, perforation and bleeding are the most important complications related to EPLBD. The hypothetical risk of perforation is higher in patients without DLBD because of direct damage to the pancreas caused by physical compression during balloon dilation.¹⁵ Additionally, according to a previous study, without DLBD is an independent risk factor for perforation.¹⁶ In contrast, the rate of pancreatitis did not differ significantly between the two groups in the present study, and there were no instances of perforation in the without-DLBD group. The rate of perforation after EPLBD in patients without DLBD is the most important concern. We suggest that our balloon inflation technique, immediate deflation of the balloon because of pain, and no further dilation, prevented perforation. Lee and Lee¹⁶ recommended gradual inflation and exercise of caution when persistent notches at the distal CBD is identified after inflation to 75% of the manufacturer's recommended maximal inflation pressure. Park *et al.*⁵ reported that if strong resistance is encountered during balloon inflation, ad-

ditional pressure should not be applied. Our technique is similar to those of Lee and Lee¹⁶ and Park *et al.*⁵ If the balloon notches do not disappear even at 75% of maximal inflation pressure, the pressure should not be increased to near maximum because nearly all patients complained of pain. In an *ex vivo* porcine model, a bile duct wall tear caused by overdilation of small bile ducts after large-balloon dilation was demonstrated.¹⁷ In humans, a tear in the lower bile duct does not necessarily lead to direct rupture into the retroperitoneum or peritoneal cavity because the lower bile duct is located within the pancreas.¹⁷ Therefore, patients without DLBD, who had an extrapancreatic bile duct that was dilated to at least the size of the stone, did not have perforation when using a balloon whose size was decided with reference to bile duct and stone diameters. In this study, all of the balloons were smaller than the maximum diameter of the bile duct outside the pancreas.

The rate of complications in the present study was lower than that of previous studies.¹⁸ In this respect, both techniques seem to be suitable for the treatment of large bile duct stones. Another possible complication is bleeding, which may be related to excessive ampullary dilation. In the present study, an episode of major bleeding after EPLBD occurred in the DLBD group. This post-ERCP bleeding was associated with damage to the small vessels surrounding the ampulla caused by the radial pressure created by balloon dilation.

There were three limitations to this study. First, the study was limited by its retrospective nature. Second, there could have been variations in balloon size and indications for EST, as the corresponding decisions were at the discretion of the endoscopist in charge. It has been suggested recently that EPLBD without EST is as safe and effective as EST alone for the removal of large bile duct stones.¹⁸⁻²⁰ Thus, there is no unified opinion about EST among endoscopists. Third, long-term complications of EPLBD such as recurrence of stones and retrograde infection were not evaluated.

We showed that EPLBD is a safe procedure in patients without DLBD. Furthermore, although the EPLBD procedure in patients without DLBD may require a long time and multiple sessions to complete the stone removal, the rate of additional ML is comparable. The lower rate of additional ML is expected to reduce the recurrence rate and procedure time when compared with EPBD. A further study comparing the effectiveness of EPLBD and EST with EPBD in patients without DLBD is needed.

In conclusion, this study shows that EPLBD is a useful and safe method for patients in whom the lower part of the bile duct is not dilated. EPLBD for patients without DLBD could dilate the lower bile duct without increasing the complications, and stone clearance rate was 100%. Our balloon inflation technique, immediate deflation of the balloon because of pain, and no further dilation, may contribute to performing safely EPLBD for patients without DLBD. There was no difference in the rate of additional ML between patients with and without DLBD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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