

[ORIGINAL ARTICLE]

Immediate or Interval Endoscopic Papillary Large-balloon Dilation after Limited Endoscopic Sphincterotomy for Bile Duct Stone Removal

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Abstract:

Objective Endoscopic papillary large-balloon dilation (EPLBD) with limited endoscopic sphincterotomy (EST) is widely used for removing multiple large common bile duct (CBD) stones. However, the safety and effectiveness of immediate EPLBD after limited EST and EPLBD at an interval after limited EST is unclear. Thus, this multicenter retrospective study was conducted to examine this matter.

Methods Propensity score-matching was performed to adjust the baseline characteristics between the immediate and interval EPLBD groups. We compared the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) complications and the early outcomes of ERCP between the 2 matched groups, which comprised 66 patients each.

Results The complete stone clearance rate in each study group was 100%. The overall incidence of post-ERCP complications in the propensity score-matched interval and immediate EPLBD groups was 3/33 (9.1%) and 1/33 (3.0%), respectively (p=0.61). The immediate EPLBD group had significantly fewer mean ERCP sessions for complete stone removal and a significantly lower rate of endoscopic mechanical lithotripsy (EML) usage than the interval EPLBD group [1.6 vs. 2.4 sessions, p<0.001; and 4/33 (12.1%) vs. 12/33 (36.4%), p=0.042, respectively].

Conclusion The incidence of post-ERCP complications in the immediate EPLBD group was not significantly different from that in the interval EPLBD group. Compared with interval EPLBD, immediate EPLBD may result in a reduced number of ERCP sessions for complete stone clearance and reduce the rate of EML usage.

Key words: common bile duct stone, endoscopic papillary large balloon dilation, complication, early outcome

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Introduction

Endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilation (EPBD) is a common standard technique for removing common bile duct (CBD) stones. However, applying EST or EPBD alone is often difficult in cases with multiple large CBD stones. Endoscopic papillary large-balloon dilation (EPLBD) using a large-diameter balloon (\geq 12 mm), which was first reported in 2003, effectively removes such difficult stones (1). EPLBD with limited EST is recommended over EPLBD without EST as per the available guidelines because EPLBD with limited EST can improve the stone clearance rate in the first endoscopic retrograde cholangiopancreatography (ERCP) session and reduce the use of endoscopic mechanical lithotripsy (EML) (2, 3). However, the safety and effectiveness of immediate EPLBD after limited EST (immediate EPLBD) and interval EPLBD

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after limited EST (interval EPLBD) is unclear.

The present multicenter retrospective study therefore conducted such a comparison.

Materials and Methods

Study design

In this multicenter retrospective study, we compared the early ERCP outcomes of immediate and interval EPLBD groups for multiple large CBD stone removal using propensity score-matching. The ethics committee of our institution approved this study. Furthermore, informed consent was obtained from each patient, assuring them that they could withdraw from the study at anytime.

Study population

This study enrolled patients with native papilla who underwent EPLBD for multiple large CBD stone removal at Kumamoto City Hospital, Kumamoto Chuo Hospital, and Saiseikai Kumamoto Hospital between April 2012 and February 2020. However, we excluded (1) those with an EST or EPBD history, (2) those with a surgically altered anatomy except for Billroth-I reconstruction, and (3) those with EPLBD without limited EST. Ultimately, this study included 190 patients; A total of 33 patients in each group were matched in one-to-one propensity score-matching.

Indications and contraindications of EPLBD

In our selected institutions, the EPLBD indications were based on the European Society of Gastrointestinal Endoscopy (ESGE) guideline and Japan Gastroenterological Endoscopy Society (JGES) guidelines for EPLBD (2, 3). EPLBD was indicated for multiple large CBD stones with CBD dilation that were difficult to remove by EST or EPBD alone. Conversely, EPLBD was contraindicated in patients with distal bile duct stricture and those without CBD dilation. In patients receiving oral antithrombotic therapy, EPLBD was performed according to the JGES guidelines for gastrointestinal endoscopy (4, 5). Based on the JGES guidelines for EPLBD, immediate EPLBD was not indicated for patients with biliary pancreatitis because of the increased risk of bile duct perforation (3). Therefore, interval EPLBD was performed after improving the condition of biliary pancreatitis in patients with biliary pancreatitis. Furthermore, interval EPLBD was performed in patients with severe cholangitis, which was diagnosed and graded with reference to the consensus criteria of the revised Tokyo guidelines 2018 (6).

Study definitions

• Immediate and interval EPLBD

Immediate EPLBD was defined as EPLBD performed immediately after limited EST in the first ERCP session. Interval EPLBD was defined as EPLBD performed in the second ERCP session and at intervals after limited EST and biliary drainage in the first session.

Post-ERCP complications

In this study, post-ERCP complications included post-ERCP pancreatitis, bleeding, cholangitis, and perforation. These complications were defined and graded according to the lexicon for endoscopic adverse events (7). In patients with biliary pancreatitis, post-ERCP pancreatitis was diagnosed as pancreatitis that met the criteria for post-ERCP pancreatitis that developed during interval EPLBD performed after improving biliary pancreatitis.

• Difficult cannulation

Difficult deep cannulation was defined as selective biliary cannulation requiring a cannulation time of >10 min (8).

Outcome measures

The outcome measures of this study were the incidence of post-ERCP complications, mean number of ERCP sessions for CBD stone removal, rates of mechanical lithotripsy, and rates of complete stone clearance.

Endoscopic procedures

After adequate sedation, 16 different endoscopists performed ERCP using a side-viewing duodenoscope (Olympus JF-260, TJF-260 V; Olympus Medical Systems, Tokyo, Japan). Five of the endoscopists were trainees with experience performing <200 ERCP procedures under the supervision of an experienced endoscopist. Contrast-assisted cannulation, guidewire-assisted cannulation, or pancreatic guidewireassisted cannulation was applied for biliary cannulation. After biliary cannulation, the position and size of the CBD stone, dilation of CBD and the absence of distal duct stricture were confirmed by cholangiography. Limited EST was performed with an incision up to medium length in the 11-12 o'clock direction. Considering the distal CBD diameter and the short diameter of the CBD stones, a 12- to 18-mm large balloon [CRE wire-guided balloon dilator (12-15, 15-18 mm), Boston Scientific Japan; Giga, Giga-II (10-12, 13-15, 16-18 mm), Century Medical, Japan; or REN (10-12, 13-15, 16-18 mm), Kaneka Medix, Japan] was selected. The large balloon was inflated slowly, and the orifice was dilated at 5-30 seconds beginning from the disappearance of the waist. In the first ERCP session, stone removal and/or biliary stent placement was performed in the immediate EPLBD group, while biliary stent placement was performed in the interval EPLBD group. In addition, in the interval EPLBD group, EPLBD and stone removal were performed in the second ERCP session at intervals until the patients' symptoms and conditions improved after the limited EST. We used a basket and/or a balloon catheter and/or EML for CBD stone removal.

Statistical analyses

We performed one-to-one propensity score-matching with a caliper and standard deviation of 0.2 to adjust the baseline characteristics between the immediate and interval EPLBD groups. Categorical and continuous data were analyzed by

Table 1. Patients' Characteristics of the Overall and Propensity-matched Cohorts.

	Overall cohort			Propensity-matched cohort		
	Interval EPLBD (n=149)	Immediate EPLBD (n=41)	p value	Interval EPLBD (n=33)	Immediate EPLBD (n=33)	p value
Age [mean (SD)] (years)	81.3 (10.6)	83.8 (9.2)	0.16	81.2 (10.2)	83.1 (9.9)	0.44
Female (%)	87 (58.4)	27 (65.9)	0.49	18 (54.5)	21 (63.6)	0.62
Normal serum bilirubin (%)	60 (40.3)	26 (63.4)	0.014	14 (42.4)	19 (57.6)	0.32
Billroth-1 reconstruction (%)	4 (2.7)	3 (7.3)	0.17	2 (6.1)	1 (3.0)	1.0
Indications of ERCP (%)						
Acute cholangitis	107 (71.8)	27 (65.9)	0.19	24 (72.7)	24 (72.7)	0.50
Biliary pancreatitis	8 (5.4)	0 (0)		1 (3.0)	0 (0)	
Obstructive jaundice without cholangitis	19 (12.8)	6 (14.6)		4 (12.1)	2 (6.1)	
Asymptomatic CBD stones	15 (10.1)	8 (19.5)		4 (12.1)	7 (21.2)	
Platelet count	19.3 (8.2)	19.7 (5.9)	0.72	19.0 (8.2)	20.0 (6.0)	0.57
PT-INR>1.5 (%)	12 (8.2)	0 (0)	0.073	0 (0)	0 (0)	1.0
Antithrombotic agents	33 (22.1)	6 (14.6)	0.40	7 (21.2)	5 (15.2)	0.75
Antibiotics (%)	129 (86.6)	37 (90.2)	0.72	31 (93.9)	29 (87.9)	0.67
Coexisting illness (%)	60 (40.3)	12 (29.3)	0.27	8 (24.2)	11 (33.3)	0.59
Peri-ampullary diverticulum (%)	62 (41.6)	20 (48.8)	0.52	19 (57.6)	15 (45.5)	0.46
Diameter of CBD [mean (SD)] (mm)	15.0 (3.3)	15.1 (4.4)	0.90	15.0 (2.8)	15.1 (4.3)	0.92
Maximum stone size [mean (SD)] (mm)	12.8 (3.8)	12.1 (4.1)	0.35	13.4 (3.9)	12.1 (4.3)	0.20
Stone number [mean (SD)]	3.9 (4.5)	4.5 (6.4)	0.57	3.1 (2.5)	4.8 (7.0)	0.19
Performance status (3 or 4) (%)	41 (27.5)	14 (34.1)	0.53	14 (42.4)	12 (36.4)	0.8
Rectal NSAIDs (%)	6 (4.0)	3 (7.3)	0.41	2 (6.1)	0 (0)	0.49
Trainees (%)	26 (17.4)	6 (14.6)	0.85	5 (15.2)	4 (12.1)	1.0
Guidewire-assisted cannulation (%)	9 (6.0)	4 (9.8)	0.48	4 (12.1)	2 (6.1)	0.67
Contrast-assisted cannulation (%)	115 (77.2)	33 (80.5)	0.81	26 (78.8)	28 (84.8)	0.75
Pancreatic guidewire-assisted cannulation (%)	16 (10.7)	4 (9.8)	1.0	3 (9.1)	3 (9.1)	1.0
Precut sphincterotomy (%)	9 (6.0)	0 (0)	0.21	0 (0)	0 (0)	1.0
Difficult cannulation (%)	32 (21.5)	7 (17.1)	0.69	4 (12.1)	5 (15.2)	1.0
Pancreatic injection (%)	53 (35.6)	15 (36.6)	1.0	13 (39.4)	11 (33.3)	0.80
Balloon (%)	123 (82.6)	32 (78.0)	0.67	29 (87.9)	26 (78.8)	0.51
Basket (%)	90 (60.4)	26 (63.4)	0.87	18 (54.5)	22 (66.7)	0.45
Prophylactic pancreatic stent placement (%)	20 (13.4)	5 (12.2)	1.0	4 (12.1)	3 (9.1)	1.0

EPLBD: endoscopic papillary large balloon dilation, SD: standard deviation, ERCP: endoscopic retrograde cholangiopancreatography, CBD: common bile duct, PT-INR: prothrombin time-international normalized ratio, NSAIDs: nonsteroidal anti-inflammatory drugs

the chi-square test/Fisher's exact test and Welch's *t*-test, respectively. Continuous data were expressed as the mean \pm standard deviation. A two-side p value <0.05 was considered statistically significant.

All data were analyzed using the EZR software program, version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing version 3.5.1, Vienna, Austria) (9).

Results

Patient characteristics

Table 1 summarizes the patient characteristics for the overall cohort and the propensity-matched cohort of both groups.

Intervals of EPLBD after limited EST

In the interval EPLBD group, the mean interval of EPLBD after limited EST was 4.5 days.

Incidence of post-ERCP complications

In the entire cohort, the overall incidence of post-ERCP complications in the interval and immediate EPLBD groups was 8/149 (5.4%) and 1/41 (2.4%), respectively (p=0.69). Table 2 presents the incidence of post-ERCP complications for the two matched groups. The groups showed no significant difference in the incidence of each complication, including bleeding, cholangitis, post-ERCP pancreatitis, and perforation.

Outcomes of ERCP

Table 3 presents the early outcomes of ERCP in the two matched groups. The rate of complete stone clearance was 100% in each group. The immediate EPLBD group had sig-

	Severity grade	Interval EPLBD (n=33)	Immediate EPLBD (n=33)	p value
Overall		3 (9.1%)	1 (3.0%)	0.61
Pancreatitis (%)	mild	2 (6.1%)	0 (0%)	0.50
Pancreatitis and perforation (%)	moderate	0 (0%)	1 (3.0%)	1.0
Cholangitis (%)	mild	1 (3.0%)	0 (0%)	1.0
Bleeding		0 (0%)	0 (0%)	1.0

Table 2. Post-ERCP Complications and the Severity Grade in the Propensity Score-matched Interval EPLBD Group and Immediate EPLBD Group.

ERCP: endoscopic retrograde cholangiopancreatography, EPLBD: endoscopic papillary large balloon dilation

Table 3. Early Outcomes of ERCP in the Propensity Score-matched Interval EPLBDGroup and Immediate EPLBD Group.

	Interval EPLBD (n=33)	Immediate EPLBD (n=33)	p value
The rate of complete stone clearance (%)	33 (100)	33(100)	1.0
Use of EML (%)	12 (36.4)	4 (12.1)	0.042
Number of ERCP sessions [mean (SD)]	2.3 (0.54)	1.6 (0.61)	< 0.001
Procedure time at first session [mean (SD)] (min)	26.7 (22.7)	30.8 (13.3)	0.18

ERCP: endoscopic retrograde cholangiopancreatography, EPLBD: endoscopic papillary large balloon dilation, EML: endoscopic mechanical lithotripsy, SD: standard deviation

nificantly fewer mean ERCP sessions for complete stone removal and a significantly lower rate of EML use than the interval EPLBD group (1.6 vs. 2.3 sessions, p<0.001; 12.1% vs. 36.4%, p=0.042, respectively). There were no significant differences in the time taken for the procedure in the first ERCP session between the 2 groups. (26.7 vs. 30.8 minutes, p=0.18).

Discussion

In this study, the incidence of post-ERCP complications and early outcomes of ERCP were compared between immediate and interval EPLBD, both after limited EST, for the removal of multiple large CBD stones. Results showed that the safety was comparable between the two EPLBD approaches. Furthermore, the immediate EPLBD group showed a reduction in the mean number of ERCP sessions for stone removal and rate of EML usage.

Current guidelines on EPLBD recommend EPLBD with limited EST (2, 3). However, the outcomes of immediate EPLBD and interval EPLBD after limited EST are unclear. We hypothesized that interval EPLBD after limited EST may increase the mean number of ERCP sessions but reduce post-ERCP complications, as compared with immediate EPLBD after limited EST, it can lessen the papillary damage that can induce post-ERCP complications. Therefore, the present study investigated and compared the incidence of post-ERCP complications and early procedural outcomes between immediate and interval EPLBD after limited EST.

According to the available guidelines (2, 3), the overall incidence of EPLBD-associated early complications is reportedly 0-22.5%, with bleeding, cholangitis, post-ERCP

pancreatitis, and perforation occurring in 0-10%, 0-5%, 0-13.2%, 0-2.5% in comparison with 1.6%, 1.1%, 2.6%, and 0.5% according to our study results, respectively. Thus, our study results were comparable to those of the current guide-lines.

A prospective observational study comparing the safety and efficacy of immediate and interval EPLBD after EST in 68 patients with acute cholangitis showed that proceduralrelated complications were rarer in the interval EPLBD group (0%) than in the immediate EPLBD group (17.1%). Overall, stone removal was successful (100%) in both groups, and both groups revealed similar rates of EML usage (22.9% in the immediate EPLBD group and 24.2% in the interval EPLBD group) (10). The results of this previous study differed from those of our own, possibly because the previous report only included patients with acute cholangitis.

In the present study, only 1 out of 33 patients experienced post-ERCP complication of moderate pancreatitis and perforation in the immediate EPLBD group. In the interval EPLBD group, 3 out of 33 patients experienced post-ERCP complications, including pancreatitis and acute cholangitis. Among these three patients, two experienced pancreatitis at the first ERCP session, and one experienced acute cholangitis after EPLBD at the second ERCP session. Nonetheless, the incidence of post-ERCP complications was comparable between the groups. Thus, fewer ERCP sessions were required by the immediate EPLBD group than by the interval EPLBD group.

Previous reports revealed that the incidence of post-ERCP complications in EPLBD with EST was comparable or lower than that with EST alone (11-15). In patients with an EST history, such as those with recurrent CBD stones, the

incidence of complications in EPLBD is extremely low (16-18). Therefore, EPLBD poses a slight additional risk of complications in addition to the risk of EST. Some explanations of these results are as follows: 1) the target of EPLBD is limited to patients with dilated CBD; 2) limited EST before EPLBD may help separate the pancreatic and biliary orifices clearly, thereby reducing the effect of papillary damage; and 3) limited EST helps reduce the chance of cutting the vessel of the papillary roof.

In our institutions, EPLBD was performed according to the ESGE and JGES guidelines for EPLBD (2, 3). However, in one patient in the immediate EPLBD group who experienced perforation, a retrospective review of the ERCP images revealed distal bile duct stricture, and a large balloon exceeding the diameter of distal CBD was used. Thus, following the current guidelines for EPLBD is important to safely perform EPLBD.

Regarding the loss of the sphincter of Oddi function after EPLBD, only limited data are available. A prospective randomized study demonstrated that EPLBD with EST and EPLBD alone resulted in a comparable loss of the sphincter of Oddi function at both one week and one year after the procedure (19). Although the degree of the loss of the sphincter of Oddi function immediately after EPLBD in the immediate and interval EPLBD groups is unknown, the reason for the low EML requirement in the immediate EPLBD group compared with that in the interval EPLBD group may involve the sphincter of Oddi, which may be more impaired in the immediate EPLBD group than in the interval EPLBD group immediately after EPLBD.

Several limitations associated with the present study warrant mention. First, as this was a retrospective study, some unmeasured confounders may be present, although the baseline characteristics were adjusted between the two groups by propensity score-matching. For example, the type of dilation balloon, diameter of dilation balloon, and length of time for EPLBD may be potential confounders. Second, the sample size of this study was limited. Third, although we performed interval EPLBD after improvement of the patients' symptoms and conditions, the optimal interval after limited EST in the interval EPLBD group was unclear in this study. Fourth, the long-term outcomes of the two groups were not examined. Further large-scale prospective studies are warranted to confirm the results of the present study.

In conclusion, immediate EPLBD after limited EST may be a safe procedure compared to interval EPLBD after limited EST. Furthermore, immediate EPLBD after limited EST may reduce the number of ERCP sessions required for complete stone clearance, and the rate of EML use may be lower than with interval EPLBD after limited EST.

The authors state that they have no Conflict of Interest (COI).

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