Original Article

Superiority of 10-mm-wide Balloon over 8-mm-wide Balloon in Papillary Dilation for Bile Duct Stones: A Matched Cohort Study

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ABSTRACT

Background/Aims: Endoscopic papillary balloon dilation (EPBD) is a possible alternative to endoscopic sphincterotomy (EST) for common bile duct (CBD) stones. To date, 10- and 8-mm EPBD have not been fully compared. **Patients and Methods:** Patients who underwent EPBD for CBD stones at two Japanese tertiary care centers between May 1994 and January 2014 were identified. Matched pairs with 10- and 8-mm EPBD were generated. Short- and long-term outcomes were compared between the two groups. **Results:** A total of 869 patients were identified (61 and 808 patients for 10- and 8-mm EPBD, respectively), and 61 well-balanced pairs were generated. The rate of complete stone removal within a single session was higher in the 10-mm EPBD group than in the 8-mm EPBD group (69% vs. 44%, $P < 0.001$), and use of lithotripsy was less frequent in the 10-mm EPBD group (23% vs. 56%, $P < 0.001$). The rates of post-ERCP pancreatitis were similar between the 10- and 8-mm EPBD groups (11% vs. 8%). Cumulative biliary complication-free rates were not statistically different between the two groups: 88% [95% confidence interval (CI): 79–97%] and 94% (95% CI: 88–100%) at 1 year and 69% (95% CI: 56–85%) and 80% (95% CI: 69–93%) at 2 years in the 10- and 8-mm EPBD groups, respectively. In the 10-mm EPBD group, ascending cholangitis was not observed, and pneumobilia was found in 5% of cases during the follow-up period. **Conclusions:** EPBD using a 10-mm balloon for CBD stones is safe and more effective than 8-mm EPBD. The sphincter function is highly preserved after 10-mm EPBD.

Key Words: Common bile duct stone, endoscopic retrograde cholangiopancreatography, lithotripsy, pancreatitis, papillary balloon dilation

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Endoscopic sphincterotomy (EST) is widely utilized as a first-line treatment option for common bile duct (CBD) stones.[1,2] However, potentially fatal complications associated with EST, such as bleeding and perforation, are not uncommon.[3,4] Furthermore, EST can cause a permanent loss of the sphincter function and resultant duodenobiliary reflux, putting patients at increased risk of long-term biliary complications including biliary stone recurrence, cholecystitis, and ascending cholangitis. Endoscopic papillary balloon dilation (EPBD) is a possible alternative to EST,[5-9] particularly in patients with coagulopathy, for example, those on antithrombotic agents,[10-12] or with liver cirrhosis,[13] or chronic renal failure on hemodialysis.[14] One of the major advantages of EPBD over EST is that EPBD potentially preserves the sphincter function[15-18] and, therefore, might reduce the risk of long-term biliary complications. Recent studies have shown a lower rate of stone recurrence after EPBD as compared with EST.[19-22]

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EPBD is usually carried out using a balloon dilation catheter with diameter up to 10 mm. Theoretically, the dilation of the ampulla using a larger balloon can ease the subsequent removal of CBD stones, with the expectation of a higher rate of successful stone removal with a lower rate of mechanical lithotripsy use. Conversely, larger EPBD may raise a legitimate concern of a greater injury to the ampulla, leading to an increased risk of procedure-related complications and stone recurrence. To date, the impact of the balloon diameter used in EPBD on the safety and efficacy for CBD stone extraction has been rarely investigated,[23] and the effectiveness of 10-mm EPBD remains to be elucidated.

In this retrospective study, we compared the short- and long-term outcomes of 10- and 8-mm EPBD for extraction of CBD stones. This study also included the long-term evaluation of the sphincter function after 10-mm EPBD.

PATIENTS AND METHODS

Study design

This study aimed to compare 10- and 8-mm EPBD to facilitate endoscopic removal of CBD stones, and was designed as a retrospective matched cohort study based on prospectively collected data. After matching patients receiving 10-mm EPBD with those receiving 8-mm EPBD considering important baseline characteristics, we compared technical success, procedure-related complications, and long-term outcomes between the groups.

This study was approved by the institutional review board in each institution and conducted according to the guidelines in the Helsinki Declaration.

Selection of patients and generation of matched pairs

From prospectively maintained databases, we identified consecutive patients who underwent 10- or 8-mm EPBD for CBD stones at the University of Tokyo Hospital and Japanese Red Cross Medical Center between May 1994 and January 2014. A balloon dilation catheter of 10 mm in diameter was introduced into our practice in March 2010. Exclusion criteria were as follows: (1) A history of EST or EPBD, (2) precut sphincterotomy or EST performed combined with EPBD, (3) previous gastrectomy with Billroth-II or Roux-en-Y reconstructions, (4) active pancreatitis at the time of endoscopic retrograde cholangiopancreatography (ERCP), (5) the diameter of CBD <8 mm, and 6) concomitant pancreatobiliary malignancy. Written informed consent for EPBD and follow-up evaluation was obtained from all patients before the procedure.

We matched patients receiving 10-mm EPBD one-to-one with those receiving 8-mm EPBD for age, sex, stone diameter, stone number, bile duct diameter, American Society of Anesthesiologists Physical Status Classification System score,[24] and gallbladder *in situ*.

Procedures of EPBD and stone removal

A side-viewing duodenoscope (JF-240, JF-260V, or TJF-260V; Olympus Optical, Tokyo, Japan) was inserted under moderate sedation. When selective biliary cannulation was achieved and CBD stones were delineated by cholangiography, the decision to perform EPBD was made. A balloon dilation catheter with a diameter of 8 or 10 mm [Eliminator; Bard Interventional Products, Billerica, MA, USA (8 mm) or Hurricane RX; Boston Scientific Corp, Natick, MA, USA (8 and 10 mm)] was inserted over the prepositioned guidewire and positioned across the papilla. Subsequently, the balloon was inflated slowly (1–2 min) with diluted contrast until the waist disappeared (the pressure was maintained not to exceed 8 atm). The pressure was maintained for 2 min initially, and thereafter, the shorter duration time of 15 s was adopted based on our previous study.[25] EPBD has been carried out with longer duration time of 5 min since its effectiveness was reported in 2010.[26]

After deflation of the balloon dilation catheter, stones were removed using a four- or eight-wire retrieval basket and/or a retrieval balloon catheter. Endoscopic mechanical lithotripsy (EML) was used to fragment large stones, as needed. Electrohydraulic lithotripsy or extracorporeal shock wave lithotripsy was used for difficult stones that could not be fragmented successfully by EML. Complete stone removal was defined as the clearance of bile duct stones confirmed by balloon-occluded cholangiography or intraductal ultrasonography.

Evaluation of short-term complications (within 30 days of EPBD)

In order to monitor procedure-related complications, each patient was routinely hospitalized at least one night after the procedure. Symptoms were continuously monitored, and a blood test including amylase was done 18–24 h after the procedure. Abdominal radiograph, ultrasound, and/or computed tomography were performed, as necessary. Short-term complications associated with EPBD were diagnosed and graded according to the consensus guidelines.[27] Therein, post-ERCP pancreatitis was defined as typical abdominal pain along with an elevated serum amylase level (≥3 times the upper limit of normal level in each institution) at more than 24 h after the procedure. The severity of pancreatitis was categorized as follows: Mild, requirement or prolongation of hospitalization for 2–3 days; moderate, hospitalization for 4–10 days; and severe, hospitalization >10 days, complicated pancreatitis, or requirement of interventions.

Evaluation of long-term outcomes (more than 30 days after EPBD)

All patients who had complete stone removal were followed up at the outpatient clinic in each institution at an interval of 6–12 months after discharge and were included in evaluation of long-term outcomes. In evaluation of long-term outcomes, the patients with failed stone removal and the corresponding matched patients were excluded. At each visit, the patients had physical examinations, blood tests, and abdominal imaging studies [ultrasonography or magnetic resonance cholangiopancreatography (MRCP)]. Other relevant examinations (e.g., endoscopic ultrasound, computed tomography, MRCP, and/or ERCP) were performed, if indicated. Biliary complications during the follow-up period were defined as a composite endpoint of bile duct stone recurrence, cholecystitis, ascending cholangitis, or liver abscess.

Pneumobilia[17] and ascending cholangitis during the follow-up period were analyzed as an indicator for the loss of the sphincter function to investigate whether larger EPBD could affect the preservation of the sphincter function.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs), and categorical variables as numbers and percentages of patients. Variables considered in matching of patients were compared between the matched groups using the Wilcoxon rank-sum test for continuous variables and the Chi-square or Fisher's exact tests for categorical variables. All other variables were compared using the Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables. Time to biliary complications was defined as the period between complete stone removal and biliary complications. Biliary complication-free survival was estimated using the Kaplan–Meier product-limit method and compared using the log-rank test.

All statistical analyses were performed using R software, version 2.15.1 (R Development Core Team: http://www.r-project.org) and its *survival* package, and matched pairs were generated based on optimal matching algorithm using its *optmatch* package. A two-sided $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Patient characteristics

The flowchart for matching patients receiving 10-mm EPBD with those receiving 8-mm EPBD is illustrated in Figure 1. Among 1227 consecutive patients without a history of EST or EPBD who underwent EPBD for CBD stones, we selected 869 eligible patients (61 for 10-mm EPBD and 808 for 8-mm EPBD). As compared with the patients with 8-mm EPBD, those with 10-mm EPBD in this cohort were older [77 (IQR: 69–85) and 72 (IQR: 63–79) in the 10- and 8-mm EPBD groups, respectively; $P < 0.001$] and were associated with a larger diameter of the largest stone [10 (IQR: 8–11) and 7 (IQR: 5–10), $P < 0.001$] and a larger number of stones [3 (IQR: 1–6) and 2 (IQR: 1–3), $P < 0.001$]. These imbalances between the unmatched 8- and 10-mm EPBD groups inferred treatment selection biases. All 61 patients with 10-mm EPBD (the 10-mm EPBD group) were successfully matched with the same number of patients with 8-mm EPBD (the 8-mm EPBD group). The demographic profiles were well balanced between the matched groups, except that the 10-mm EPBD group was more likely to take antithrombotic agents as compared with the 8-mm EPBD group [Table 1].

Procedures of stone removal in the matched 10- and 8-mm EPBD groups

The outcomes of stone removal by EPBD are summarized in Table 2. The rate of complete stone removal did not differ significantly between the 10- and 8-mm EPBD groups (97% vs. 100%, $P = 0.480$). However, the rate of complete stone removal within a single session was significantly higher in the 10-mm EPBD group as compared with the 8-mm EPBD group (69% vs. 44%, $P < 0.001$), and the rate of requirement of lithotripsy of any type was significantly lower (23% vs. 56%, $P < 0.001$). As a result, a smaller number of ERCP sessions were required in the 10-mm EPBD group than in the 8-mm EPBD group [1 (IQR: 1–1.5) and 2 (IQR: 1–2), $P < 0.001$]. Complete stone removal failed in two patients in the 10-mm EPBD group; one underwent

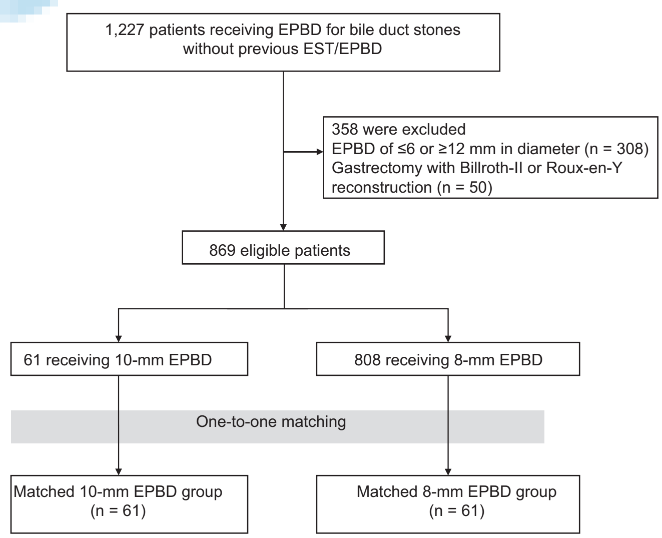

Figure 1: Flowchart for generating 61 matched pairs with 10- or 8-mm EPBD for extraction of bile duct stones. Patient matching was done using optimal matching algorithm with the following variables: Age, sex, stone diameter, stone number, bile duct diameter, American Society of Anesthesiologists Physical Status Classification System score and a history of cholecystectomy. EPBD, endoscopic papillary balloon dilation; EST, endoscopic sphincterotomy

Table 1: Patient characteristics of the matched pairs with 10- and 8-mm EPBD for bile duct stone removal

Variables	*n*=61		*P*
	10-mm EPBD	8-mm EPBD	
Patient factor			
Sex[a], male/female	38/23 (62/38)	38/23 (62/38)	1.000
Age[a], years	77 (69-85)	75 (69-82)	0.205
ASA score[a], 1/2/3/4/5-6	25/27/7/2/0 (41/45/11/3/0)	22/30/8/1/0 (36/49/13/2/0)	0.862
Peripapillary diverticulum	30 (49)	32 (52)	0.874
Previous Billroth-I gastrectomy	2 (3)	8 (13)	0.114
Gallbladder *in situ*[a]	48 (79)	49 (80)	0.825
Gallbladder stone	39 (64)	36 (59)	0.663
Previous pancreatitis	3 (5)	5 (8)	0.683
Users of antithrombotic agents[b]	12 (20)	2 (3)	0.009
Aspirin	7 (11)	2 (3)	
Clopidogrel	1 (2)	0	
Warfarin	4 (7)	0	
Stone factor			
Diameter of the largest stone[a], mm			
≤6/7-8/9-10/≥11	5/16/23/17 (8/26/38/28)	5/16/23/17 (8/26/38/28)	1.000
Number of stones[a]			
1/2-3/≥4	20/16/25 (33/26/41)	23/18/20 (37/30/33)	0.643
Diameter of the CBD[a], mm			
≤8/9-12/≥13	2/45/14 (3/74/23)	2/43/16 (3/71/26)	0.915

Numerical data are expressed as the number of patients (%) or median (interquartile range). [a]These variables considered in patient matching were compared using non-paired statistical tests, and all other variables were compared using paired tests. [b]All patients discontinued antithrombotic agents during the periprocedural period of EPBD. ASA: American Society of Anesthesiologists, CBD: Common bile duct, EPBD: Endoscopic papillary balloon dilation

Table 2: Outcomes of endoscopic removal of bile duct stones and short-term complications in the matched 10- and 8-mm EPBD groups

	n=61		*P*
	10-mm EPBD	8-mm EPBD	
Procedures			
Complete stone removal	59 (97)	61 (100)	0.480
Number of ERCP sessions			
1	46 (76)	28 (46)	0.002
2	13 (21)	28 (46)	
≥3	2 (3)	5 (8)	
Use of lithotripsy			
Overall	14 (23)	34 (56)	<0.001
Mechanical lithotripsy	13 (21)	34 (56)	
ESWL	1 (2)	0	
EHL	0	0	
Prophylactic pancreatic stent for post-ERCP pancreatitis	2 (3)	1 (2)	1.000
Short-term complications			
Overall	11 (18)	8 (13)	0.606
Pancreatitis	7 (11)	5 (8)	0.724
Mild/moderate/severe[a]	5/2/0 (8/3/0)	3/2/0 (5/3/0)	1.000
Cholangitis	5 (8)	3 (7)	0.724
Cholecystitis	0	1 (2)	1.000
Bleeding	0	0	
Perforation	0	0	
Basket impaction	0	0	
Others	0	1 (2)	1.000
Pancreatic duct stricture	0	1 (2)	1.000

Numerical data are expressed as the number of patients (%). [a]A *P* value for this cell was computed by the Fisher's exact test. EHL: Electrohydraulic lithotripsy, EPBD: Endoscopic papillary balloon dilation, ERCP: Endoscopic retrograde cholangiopancreatography, ESWL: Extracorporeal shock wave lithotripsy

plastic biliary stent placement and the other underwent open choledochotomy at the patient's request after the first session of ERCP.

Short-term complications of the matched 10- and 8-mm EPBD groups

The short-term complications within 30 days of stone removal by EPBD are presented in Table 2. The rates of post-ERCP pancreatitis were similar in the 10- and 8-mm groups (11% vs. 8%, $P = 0.724$), and all patients with pancreatitis could be managed conservatively. Severe pancreatitis was not encountered in either group and the severity of pancreatitis did not depend on the treatment assignment.

No patients in both groups developed bleeding or perforation. Overall, the rates of short-term complications after EPBD were comparable (18% vs. 13% in the 10- and 8-mm EPBD groups, respectively; $P = 0.606$).

Long-term outcomes of the matched 10- and 8-mm EPBD groups

When evaluating long-term outcomes after EPBD, we excluded two pairs which included two patients with unsuccessful complete stone removal and, therefore, analyzed 59 pairs. Among 47 patients with gallbladder at the time of 10-mm EPBD, cholecystectomy was performed after EPBD in 17 patients (36%), gallbladder left *in situ* with stones in 24 (51%), and gallbladder left *in situ* without stones in 6 (13%). Among 49 patients with gallbladder at the time of 8-mm EPBD, cholecystectomy was performed after EPBD in 16 patients (33%), gallbladder left *in situ* with stones in 20 (41%), and gallbladder left *in situ* without stones in 13 (27%). Gallbladder left *in situ* with stones after EPBD was seen in 41% versus 34% patients in the 10- and 8-mm EPBD groups, respectively ($P = 0.522$). The median follow-up time was 2.0 (IQR: 0.7–3.1) and 2.8 (IQR: 1.3–5.3) years in the 10- and 8-mm EPBD groups, respectively ($P < 0.001$).

Table 3 presents the details of long-term biliary complications observed after EPBD. Overall, the rates of long-term biliary

Table 3: Long-term outcomes of the patients with successful complete stone removal by 10- and 8-mm EPBD

Biliary complication	*n*=59		*P*
	10-mm EPBD	8-mm EPBD	
Overall	14 (24)	12 (20)	0.823
Bile duct stone recurrence	12 (20)	10 (17)	0.814
Ascending cholangitis	0	0	NA
Cholecystitis[a]	2 (7)	2 (6)	1.000
Liver abscess	0	0	NA

Numerical data are expressed as the number of patients (%). [a]Percentages were calculated including 30 and 33 patients with gallbladder left *in situ* after 10- and 8-mm EPBD, respectively. EPBD: Endoscopic papillary balloon dilation, NA: Not available

complications were not significantly different between the groups (24% vs. 20% for 10- and 8-mm EPBD, respectively; $P = 0.823$). Bile duct stone recurrence was observed in 12 (20%) and 10 (17%) patients in the 10- and 8-mm EPBD groups, respectively ($P = 0.814$). Ascending cholangitis without stone recurrence was not observed in both groups. No significant difference in biliary complication-free survival was found between the two groups ($P = 0.239$) [Figure 2]. The biliary complication-free rates were estimated to be 88% [95% confidence interval (CI): 79–97%] and 94% (95% CI: 88–100%) at 1 year and 69% (95% CI: 56–85%) and 80% (95% CI: 69–93%) at 2 years in the 10- and 8-mm EPBD groups, respectively. All patients with bile duct stone recurrence were successfully managed by repeated ERCP, except one patient in whom asymptomatic bile duct stones were left untreated.

Pneumobilia was evaluated during the follow-up period. Any of the abdominal imaging studies was performed in 39 (66%) and 37 (63%) patients in the 10- and 8-mm EPBD groups, respectively. The rate of pneumobilia after 10-mm EPBD was not significantly higher than that after 8-mm EPBD (5% and 8%, $P = 0.671$).

DISCUSSION

In this matched cohort study based on data derived from two Japanese tertiary care centers, as compared with 8-mm EPBD, 10-mm EPBD was associated with a higher rate of complete stone removal within a single session and less frequent use of EML without increasing the risk of post-ERCP pancreatitis. Furthermore, our study demonstrated that the sphincter function could be preserved after 10-mm EPBD as after 8-mm EPBD, which ensures one of the major advantages of EPBD over EST.

EPBD is utilized as an alternative to EST for endoscopic stone extraction,[5-9] particularly in patients with coagulopathy. Although the efficacy of endoscopic papillary large balloon

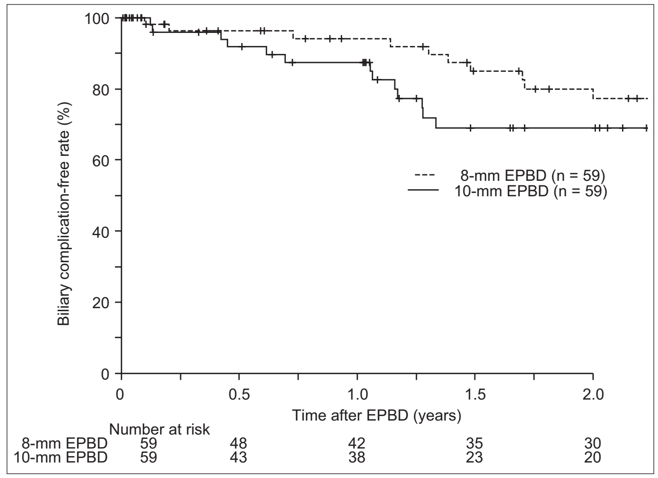

Figure 2: Kaplan-Meier curves showing biliary complication-free survival of the patients with successful stone removal in the matched 10- and 8-mm EPBD groups. Small vertical bars on each curve indicate censored cases. EPBD, endoscopic papillary balloon dilation

dilation (EPLBD) using a ≥12-mm balloon dilation catheter has been recently reported,[28-31] this procedure cannot be applied for small or normal bile duct and might cause a permanent loss of the sphincter function similar to EST, leading to an increased risk of stone recurrence. Taken together, EPBD can be a first-choice option for CBD stones in a subset of patients. To date, however, the outcomes of EPBD for CBD stones have not been fully investigated according to the size of a balloon dilation catheter. In a retrospective study of 208 patients, Li *et al.*, evaluated the outcomes of EPBD with different-sized balloons (8–14 mm), which were matched for the size of the largest stone.[23] The investigators successfully removed bile duct stones in all cases regardless of the stone size, and found no significant association between the balloon size and post-ERCP pancreatitis. However, in addition to the fact that a limited EST was performed prior to EPBD, the adjustment for baseline characteristics between the groups with different-sized balloons was not done because it was not their study aim. Therefore, only limited data on comparison of 10- and 8-mm balloons in EPBD alone are currently available, considering the trade-off of technical success and complications.

The present study demonstrated the superiority of 10-mm EPBD over 8-mm EPBD as a means of sphincteroplasty to facilitate endoscopic stone extraction. Based on the promising results of several series about EPLBD without EST,[31-33] a highly enlarged orifice of the bile duct by a larger balloon can make subsequent procedures efficient, because it potentially eases device insertion and stone extraction. In our study, 10-mm EPBD was shown to increase the rate of complete stone removal within a single session and decrease the rate of requirement of lithotripsy. Given no increase in the short- and long-term complications in our 10-mm EPBD group as discussed below, 10-mm EPBD is considered as the more preferable sphincteroplasty than 8-mm EPBD in cases with bile duct greater than 10 mm.

Post-ERCP pancreatitis remains a serious issue associated with endoscopic extraction of bile duct stones.[34-36] The pathogenesis of pancreatitis after EPBD is not fully understood, but EPBD itself or subsequent stone extraction procedure might provoke papillary edema or spasm, leading to the outflow obstruction of pancreatic juice and eventually the development of pancreatitis. Although use of a larger balloon in EPBD might increase the injury to the ampulla, the rates of post-ERCP pancreatitis did not differ significantly between our 10- and 8-mm EPBD groups. We speculate that 10-mm EPBD might make stone extraction easier and could outweigh the increased damage to the ampulla.

The high rates of post-ERCP pancreatitis in our 10- and 8-mm EPBD groups needs to be discussed in context, regardless of the fact that no patients developed severe pancreatitis. EPBD is considered to be associated with a higher rate of post-ERCP pancreatitis, as compared with EST.[7,37] The relatively high rate of this complication in our study might be explained by more difficult cases referred to tertiary care centers and the involvement of trainee endoscopists. Presumably, pharmaceutical prevention[38,39] and pancreatic stent placement[40] should be administered more intensively than was done in our study, to minimize the risk of pancreatitis after EPBD. Other complications including bleeding and perforation which might be increased by the increase of balloon diameter were not observed in the 10-mm EPBD group. Taking the reported safety of EPLBD into account,[28-33] use of a larger balloon is considered acceptably safe, as far as the diameter of the balloon used does not exceed that of the lower bile duct.

The most notable advantage of EPBD is that this procedure potentially preserves the sphincter function, as opposed to EST.[15-18] Preservation of the sphincter function can prevent the duodenobiliary reflux and the recurrence of biliary stones due to bacterial colonization.[41] In terms of the preservation of the sphincter function, there is a concern about use of a larger balloon in EPBD, which might compromise the sphincter function more frequently. Li *et al.* found a significant correlation between increased balloon size and the rate of long-term post-ERCP pneumobilia.[23] Pneumobilia during the follow-up period was uncommon in our 10-mm EPBD group, and ascending cholangitis was not observed. There were no significant differences between the long-term biliary complications in our 10- and 8-mm EPBD groups, and a further prospective investigation is warranted about the threshold of balloon size to preserve the sphincter function after EPBD.

Several limitations should be acknowledged in the present study. The retrospective and, thus, non-randomized design was the major drawback of this study. Though patient matching was performed to control treatment selection bias, unmeasured confounding factors could not be adjusted. A relatively small number of patients and the shorter follow-up time in the 10-mm EPBD group should also be noted. Therefore, a randomized control trial with a large sample size is required to confirm the advantages of 10-mm EPBD over 8-mm EPBD. Various EPBD methods used in this study with regard to the duration of dilation and the types of balloon dilation catheters were the other limitations.

CONCLUSION

In conclusion, 10-mm EPBD is a safe procedure which allows more efficient endoscopic extraction of CBD stones, as compared with 8-mm EPBD. Furthermore, the sphincter function can be highly preserved after 10-mm EPBD, which ensures comparable long-term outcomes to 8-mm EPBD.

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