Multicenter randomized trial of endoscopic papillary large balloon dilation without sphincterotomy versus endoscopic sphincterotomy for removal of bile duct stones: MARVELOUS trial

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ABSTRACT

Background Endoscopic papillary large balloon dilation (EPLBD) has been increasingly used for the management of large common bile duct (CBD) stones. Although EPLBD is often preceded by endoscopic sphincterotomy (EST), EPLBD alone without EST has been increasingly reported as an alternative to EST for large CBD stones.

Methods This multicenter randomized trial was conducted at 19 Japanese institutions to compare the efficacy and safety of EPLBD alone versus EST for the removal of large (≥ 10 mm) CBD stones. The primary end point was complete stone removal in a single session. The secondary end points included: overall complete stone removal, lithotripsy use, procedure time, adverse events, and cost.

Results 171 patients with large CBD stones were included in the analysis. The rate of single-session complete stone removal was significantly higher in the EPLBD-alone group than in the EST group (90.7 % vs. 78.8 %; $P = 0.04$). Lithotripsy use was significantly less frequent in the EPLBD group than in the EST group (30.2 % vs. 48.2 %; $P = 0.02$). The rates

of early adverse events were comparable between the two groups: rates of overall adverse events were 9.3 % vs. 9.4 % and of pancreatitis were 4.7 % vs. 5.9 % in the EPLBD and EST groups, respectively. The procedure costs were $1442 vs. $1661 in the EPLBD and EST groups, respectively ($P = 0.12$).

Conclusion EPLBD without EST for the endoscopic treatment of large CBD stones achieved a significantly higher rate of complete stone removal in a single session compared with EST, without increasing adverse events.

Introduction

Endoscopic sphincterotomy (EST) is the current standard for the treatment of common bile duct (CBD) stones [1]. Endoscopic papillary balloon dilation (EPBD), first introduced by Staritz et al. in 1983 [2], is a possible alternative [3, 4], but it is reportedly associated with an increase in post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) [5 – 7] and is now performed only in selected cases with altered anatomy or coagulopathy [8 – 11]. While late biliary events are less common after EPBD because it preserves the function of the sphincter of Oddi [12, 13], it is also associated with the use of lithotripsy, especially in patients with large CBD stones.

Endoscopic papillary large balloon dilation (EPLBD) has been increasingly used to manage those with large CBD stones [14 – 17]. While EPLBD is often preceded by EST, EPLBD without EST reportedly provides comparable outcomes [18, 19]. However, few data are available on a comparison between EPLBD without EST and EST alone. If EST can be omitted prior to EPLBD, it would be favorable in terms of the risk of bleeding [20], as well as cost-effectiveness. Therefore, we conducted this multicenter randomized controlled trial (RCT) of EPLBD without EST and EST for the endoscopic treatment of large CBD stones.

Methods

Study design

This was a prospective multicenter RCT conducted in 19 Japanese centers. The study was approved by the ethical committee at each center and written informed consent was obtained from all patients. The study was registered at UMIN clinical trial registration (UMIN000010012).

Patients

Consecutive patients aged 60 years or older who were scheduled for ERCP for the management of large CBD stones (≥ 10 mm in maximum diameter) were enrolled in the study. To allow the use of EPLBD, the size of the distal CBD needed to be ≥ 12 mm without distal biliary stricture. Patients with a plastic stent or a nasobiliary drainage tube who had not undergone ampullary intervention were also included. Those with a previous history of ampullary interventions or gastrectomy with Roux-en-Y or Billroth II reconstruction, acute biliary pancreatitis, severe acute cholangitis, severe coagulopathy, or general conditions that would make them unfit for surgery were excluded.

Interventions

EPLBD without EST

After deep biliary cannulation had been achieved, EPLBD with a balloon catheter (CRE wire-guided biliary dilation balloon catheter, Boston Scientific Japan, Tokyo, Japan; or GIGA EPLBD balloon, Century Medical Inc., Tokyo, Japan) was performed without a preceding EST. The extent of balloon dilation was determined according to the size of the stones, but did not exceed the diameter of the distal CBD. The balloon was inflated slowly (1 – 2 minutes) under endoscopic and fluoroscopic guidance and was deflated immediately after the disappearance of the balloon waist (▶ **Fig. 1**).

Patients with a distal biliary stricture or without bile duct dilatation on cholangiogram underwent crossover to EST. In addition, when CBD stones were impacted in the ampulla or located in the distal end of the CBD, attempts were made to push the stones further into the CBD to avoid bile duct perforation during EPLBD. When this was technically impossible, EPLBD was not performed.

EST

After deep cannulation had been achieved, EST was performed with a pull-type sphincterotome. The length of EST was either full (up to the transverse duodenal fold) or mid (about two-thirds of the full EST).

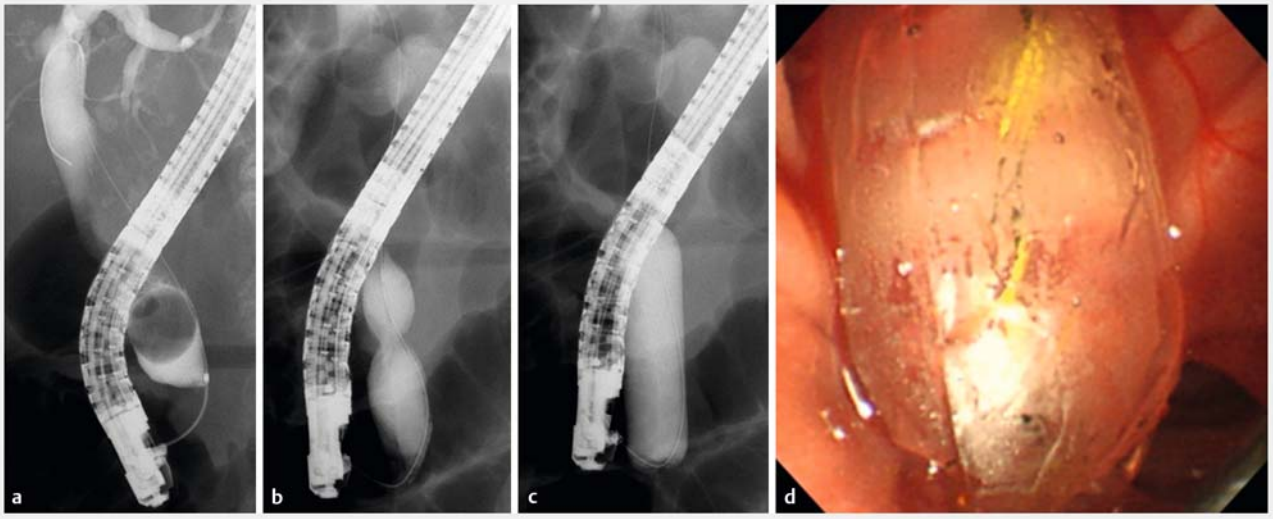
Outcome measurements

Two-step analyses were planned a priori. The first-step analysis was to evaluate short- term outcomes, such as the efficacy of stone removal, and the second-step analysis was to evaluate long-term outcomes, such as late biliary events. In this paper, we report the analysis of the first-step short-term outcomes.

The primary outcome was the rate of complete stone removal in a single session. Secondary outcomes were the rates of: overall complete stone removal, the use of lithotripsy, procedure time, early adverse events, and procedure costs.

Definitions

Complete stone removal was defined as no filling defects on occlusion cholangiogram. Procedure time was defined as the time from deep biliary cannulation to the occlusion cholangiogram. Early adverse events were defined and graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon [21]. The procedure cost included the cost of the ERCP and the devices used for EST, EPLBD, and stone extraction. We did not include the cost of hospitalization because it would have varied within the participating institutions.



▶ **Fig. 1** Images of endoscopic papillary large balloon dilation. **a – c** Cholangiographic images showing: **a** a large bile duct stone; **b** a large balloon being slowly dilated under endoscopic and fluoroscopic guidance; **c** the fully dilated balloon with its waist having disappeared. **d** Endoscopic view of large balloon dilation.

Statistical analyses

We hypothesized a 20 % difference in the rate of complete stone removal in a single session (70 % in the EST group and 90 % in the EPLBD group) and the sample size calculation was performed with a type I error of 0.05 (two-sided) and a power of 0.8. A total sample size of 180 patients (90 in each group) was required, including a 5 % drop-out rate.

Randomization was done centrally prior to the ERCP using a minimization computer algorithm, stratified by centers and the estimated size of the CBD stone prior to ERCP (< 15 mm vs. ≥ 15 mm). Patients were randomly assigned to undergo EST or EPLBD for endoscopic removal of their large CBD stones. Group assignment was not masked from either the patients or the investigators. Modified intention-to-treat analysis was performed after excluding those patients who did not undergo endoscopic stone extraction.

Categorical variables were compared using the chi-squared test or Fisher's test, and continuous variables were compared using the Student's *t* test or Wilcoxon test. All tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP version 12.0 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients

A total of 181 patients were enrolled between February 2013 and January 2015 in 19 Japanese institutions, with 91 being randomized to the EPLBD group and 90 to the EST group (▶ **Fig. 2**). After the exclusion of 10 patients, 171 patients (86 in the EPLBD group and 85 in the EST group) were eventually included in the analysis.

The characteristics of the 171 analyzed patients are shown in ▶ **Table 1**. Although the mean diameter of the largest stone did not differ between the two groups, the rate of CBD stone size > 15 mm on cholangiogram was higher in the EPLBD group. Otherwise, there were no significant differences between the two groups.

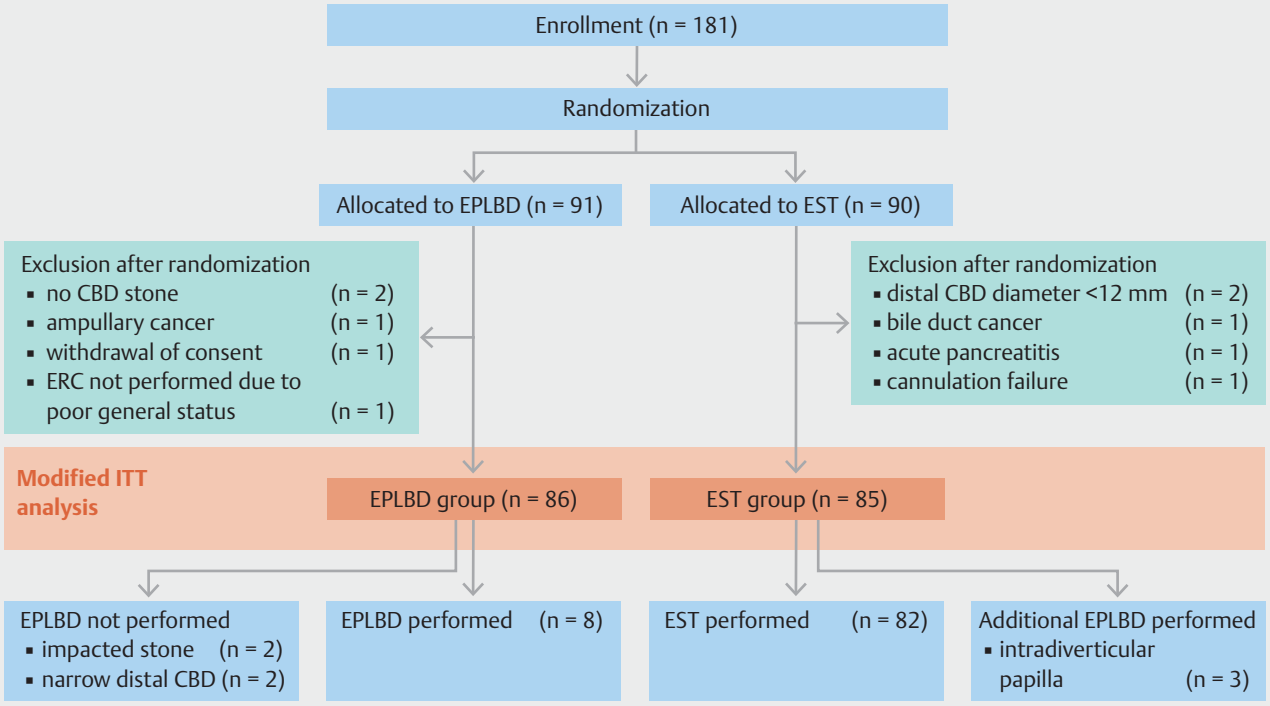
Seven patients did not undergo the allocated interventions. Four patients in the EPLBD group underwent EST because of an impacted stone (n = 2) or narrow distal CBD (n = 2). Three patients in the EST group underwent additional EPLBD because an EST was insufficient owing to an intradiverticular papilla.

Efficacy of stone removal

The efficacy of stone removal is summarized in ▶ **Table 2**. The rate of complete stone removal in a single session was significantly higher in the EPLBD group: 90.7 % (78/86) vs. 78.8 % (67/85) in the EST group (odds ratio [OR] 2.62, 95 % confidence interval [CI] 1.07 – 6.41; $P = 0.04$). Overall complete stone removal rates were 100 % (86/86) in the EPLBD group and 95.3 % (81/85) in the EST group ($P = 0.06$).

Despite the higher rate of stones larger than 15 mm in size in the EPLBD group, the use of lithotripsy was infrequent in the EPLBD group: 30.2 % (26/86) in the EPLBD group and 48.2 % (41/85) in the EST group (OR 0.47, 95 %CI 0.25 – 0.87; $P = 0.02$). However, rates of complete stone removal using a single device were not high in either group: < 5 % by basket catheter alone and about 30 % by balloon catheter alone.

The mean (standard deviation) total procedure time was not significantly different between the two groups (52.6 [58.4] minutes in the EPLBD group and 49.6 [39.7] minutes in the EST group). The procedure cost was higher in the EST group ($1661 vs. $1442 in the EPLBD group), though this was not statistically significant ($P = 0.12$).



▶ **Fig. 2** Patient flowchart from study enrollment to analysis. EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; CBD, common bile duct; ITT, intention to treat.

▶ **Table 1** Characteristics of the 171 analyzed patients who were randomized to either endoscopic papillary large balloon dilation (EPLBD) or endoscopic sphincterotomy (EST) to treat their large common bile ducts stones.

	EPLBD alone (n = 86)	**EST (n = 85)**	***P* value**
Age, mean (SD), years	79.1 (8.1)	80.9 (8.2)	0.13
Sex, male, n (%)	38 (44.2 %)	41 (48.2 %)	0.65
ASA score, n (%)			
▪ 1	15 (17.4 %)	8 (9.4 %)	0.31
▪ 2	62 (72.1 %)	65 (76.5 %)	
▪ 3	9 (10.5 %)	11 (12.9 %)	
Previous cholecystectomy, n (%)	12 (14.0 %)	10 (11.8 %)	0.82
Prior ERCP, n (%)	36 (41.9 %)	42 (49.4 %)	0.36
Number of stones, n (%)			
▪ 1	34 (39.5 %)	27 (31.8 %)	0.54
▪ 2 or 3	27 (31.4 %)	29 (34.1 %)	
▪ ≥4	25 (29.1 %)	29 (34.1 %)	
Maximum stone size, mean (SD), mm	15.2 (4.6)	14.3 (4.8)	0.22
CBD stone size ≥ 15 mm, n (%)	41 (47.7 %)	26 (30.6 %)	0.03
CBD diameter, mean (SD), mm	16.4 (3.6)	16.0 (4.0)	0.44
Periampullary diverticulum, n (%)	48 (55.8 %)	57 (67.1 %)	0.16

SD, standard deviation; ASA, American society of anesthesiologists; ERCP, endoscopic retrograde cholangiography; CBD, common bile duct.

▶ **Table 2** Outcomes of endoscopic papillary large balloon dilation (EPLBD) and endoscopic sphincterotomy (EST) in the total cohort.

	EPLBD alone (n = 86)	EST (n = 85)	*P* value
Single-session stone removal, n (%)	78 (90.7 %)	67 (78.8 %)	0.04
Overall complete stone removal, n (%)	86 (100.0 %)	81 (95.3 %)	0.06
Sessions for complete stone removal, n (%)			
▪ 1	78 (90.7 %)	67 (78.8 %)	0.09
▪ 2	3 (3.5 %)	11 (12.9 %)	
▪ 3	2 (2.3 %)	1 (1.2 %)	
▪ 4	3 (3.5 %)	2 (2.4 %)	
Stone removal by basket alone, n (%)	3 (3.5 %)	4 (4.7 %)	0.72
Stone removal by balloon alone, n (%)	24 (27.9 %)	27 (31.8 %)	0.62
Use of lithotripsy, n (%)	26 (30.2 %)	41 (48.2 %)	0.02
▪ EML	26 (30.2 %)	41 (48.2 %)	
▪ ESWL	1 (1.2 %)	1 (1.2 %)	
Total procedure time, mean (SD), minutes	52.6 (58.4)	49.6 (39.7)	0.70
Time for stone clearance, mean (SD), minutes	42.3 (53.4)	42.7 (38.1)	0.96
Procedure cost, mean (SD), US$	1442 (857)	1661 (942)	0.12

SD, standard deviation; EML, endoscopic mechanical lithotripsy; ESWL, extracorporeal shockwave lithotripsy; US$, US dollar.

Subgroup analysis of the 67 patients who had stones larger than 15 mm is shown in ▶ **Table 3**. The complete stone removal rate in a single session was higher in the EPLBD group at 85.4 % (35/41) compared with 53.8 % (14/26) in the EST group (OR 5.0, 95 %CI 1.57 – 15.94; *P* = 0.01) in this subgroup too. An absolute difference in the complete stone removal rate between the EPLBD and EST groups was more prominent in those patients with > 15-mm CBD stones: 31.6 % compared with 11.9 % in the total cohort. Lithotripsy was more often necessary in this subgroup, but the rate was still lower in the EPLBD group: 43.9 % (18 /41) in the EPLBD group vs. 69.2 % (18/26) in the EST group (OR 0.35, 95 % CI 0.12 – 0.98; *P* = 0.05).

Safety

The early adverse events that occurred are shown in ▶ **Table 4**. The rates of overall adverse events, including PEP, were comparable: 9.3 % (8/86) in the EPLBD group and 9.4 % (8/85) in the EST group. PEP occurred in four patients (4.7 %) in the EPLBD group and five (5.9 %) in the EST group. Most of the cases of PEP were mild, and no patients in either group developed severe PEP. There was no mortality observed within 30 days in the study cohort.

Discussion

EPLBD is now one of the treatment options for the endoscopic removal of large CBD stones [17]. While EPLBD is often preceded by EST, some studies have shown that EPLBD without EST can provide comparable clinical outcomes [18, 19]. Our study demonstrated a better efficacy for EPLBD without EST compared with EST for the endoscopic management of patients with large CBD stones. EPLBD without EST achieved a high complete stone removal rate in a single session, without increasing the number of early adverse events such as PEP.

Several prospective comparative studies [22 – 31] have been conducted on EPLBD, both with and without EST (▶ **Table 5**). There were no significant differences in overall complete stone removal in any of these studies, but two studies [28, 29] demonstrated a higher rate of complete stone removal in a single session for EPLBD with EST compared with EST. There were two studies [24, 26] that compared EPLBD without EST and EST, but our study was the first study to show the superiority of EPLBD without EST over EST, with complete stone removal rates in a single session of 90.7 % in the EPLBD group and 78.8 % in the EST group (*P* = 0.04). Of note, the difference was more prominent in the subgroup of patients with CBD stones of 15 mm or more in size.

While overall complete stone removal was achieved in more than 95 %, regardless of the type of ampullary intervention in most studies, single-session stone removal rates varied among studies from 71.4 % to 100 %. An interstudy comparison might be difficult because of these differences, which may be attributable to the different indications, including the size of CBD stones, and the procedure length. For example, contrary to our study results, a randomized controlled trial by Teoh et al. [26] showed similar efficacy, other than for the use of endoscopic mechanical lithotripsy (EML), between EPLBD with preceding EST and EST alone. However, their study was conducted

▶ **Table 3** Outcomes of endoscopic papillary large balloon dilation (EPLBD) and endoscopic sphincterotomy (EST) in those patients who had stones larger than 15 mm.

	EPLBD alone (n = 41)	EST (n = 26)	*P* value
Single-session stone removal, n (%)	35 (85.4 %)	14 (53.8 %)	0.01
Overall complete stone removal, n (%)	41 (100.0 %)	24 (92.3 %)	0.15
Sessions for complete stone removal, n (%)			
▪ 1	35 (85.4 %)	14 (53.8 %)	< 0.01
▪ 2	2 (4.9 %)	9 (34.6 %)	
▪ 3	1 (2.4 %)	0	
▪ 4	3 (7.3 %)	1 (3.8 %)	
Use of lithotripsy, n (%)	18 (43.9 %)	18 (69.2 %)	0.05
▪ EML	18 (43.9 %)	18 (69.2 %)	
▪ ESWL	1 (2.4 %)	1 (3.8 %)	
Total procedure time, mean (SD), minutes	66.1 (73.1)	62.9 (44.8)	0.83
Time for stone clearance, mean (SD), minutes	53.6 (68.3)	54.7 (41.4)	0.94

EML, endoscopic mechanical lithotripsy; ESWL, extracorporeal shockwave lithotripsy; SD, standard deviation.

▶ **Table 4** Number of early adverse events in the total cohort of patients who underwent endoscopic papillary large balloon dilation (EPLBD) or endoscopic sphincterotomy (EST).

	EPLBD alone (n = 86)	EST (n = 85)	*P* value
Overall	8 (9.3 %)	8 (9.4 %)	1
Pancreatitis	4 (4.7 %)	5 (5.9 %)	0.75
▪ Mild	3 (3.5 %)	4 (4.7 %)	
▪ Moderate	1 (1.2 %)	1 (1.2 %)	
▪ Severe	0	0	
Bleeding	0	1 (1.2 %)	0.50
Perforation	0	0	
Cholangitis	3 (3.5 %)	2 (2.4 %)	1
Cholecystitis	0	0	
Pneumonia	1 (1.2 %)	1 (1.2 %)	1
Mortality	0	0	

in only two centers and 82 % of patients were enrolled in just one of these; the inclusion criteria were CBD size ≥ 13 mm and the minimum stone size was also 13 mm. Meanwhile, our study was performed in 19 centers and patients with CBD stones of ≥ 10 mm were enrolled. Furthermore, the balloon size was up to 15 mm in the previous study, but we selected the balloon size according to the size of distal CBD and a > 15-mm balloon was also used. At least, EPLBD without EST does not appear to be inferior to EST or to EPLBD with EST according to the currently available evidence [15].

PEP is one of the most common adverse events after CBD stone removal, which can be lethal if severe. EPLBD, either with or without EST, does not appear to increase the risk of PEP. In patients with large CBDs, the risk of PEP may be low because of the large size of their CBDs, but also because such patients tend to be older [32]. Our study cohort, which consisted of patients aged ≥ 60 years and with a CBD diameter ≥ 12 mm, would be considered to have a low risk of PEP. In one study [23] that compared EPLBD with EST and EST, the incidence of overall adverse events was higher after EST because of a signif-

▶ **Table 5** Summary of randomized controlled trials of endoscopic papillary large balloon dilation (EPLBD) with or without endoscopic sphincterotomy (EST) vs. EST.

Authors	Interventions	n	Single-session stone removal	Overall stone removal	Use of EML	Adverse events	PEP
Heo et al. 2007 [22]	EPLBD with EST	100	83 %	97 %	8.0 %	5 %	4 %
	EST	100	87 %	98 %	9.0 %	7 %	4 %
Stefanidis et al. 2011 [23]	EPLBD with EST	45	100.0 %	NA	NA[1]	4.4 %[2]	2.2 %
	EST	45	91.1 %	NA	NA	20.0 %[3]	2.2 %
Oh et al. 2012 [24]	EPLBD alone	40	82.5 %	97.5 %	10.0 %	NA	5.0 %
	EST	43	81.4 %	95.3 %	20.9 %	NA	7.0 %
Hwang et al. 2013 [25]	EPLBD alone	62	91.9 %	96.8 %	16.2 %	6.5 %	6.5 %
	EPLBD with EST	69	94.2 %	95.7 %	21.8 %[4]	7.2 %	4.3 %
Teoh et al. 2013 [26]	EPLBD with EST	73	89.0 %	97.2 %	28.8 %[2]	6.8 %	2.7 %
	EST	78	88.5 %	100.0 %	46.2 %	10.3 %	3.8 %
Guo et al. 2015 [27]	EPLBD alone	85	91.8 %	NA	14.1 %	4.7 %	2.4 %
	EPLBD with EST	85	96.5 %	NA	8.2 %	5.9 %	2.4 %
	EST	85	92.9 %	NA	9.4 %	4.7 %	2.4 %
Karsenti et al. 2017 [28]	EPLBD with EST	77	96.1 %[2]	96.1 %	3.9 %[2]	8.1 %	1.4 %
	EST	73	74.0 %	94.5 %[5]	35.6 %	9.3 %	0.0 %
Omar et al. 2017 [29]	EPLBD with EST	61	86.9 %[2]	96.7 %	9.8 %[2]	NA	4.9 %
	EST	63	71.4 %	93.7 %	17.5 %	NA	6.3 %
Cheon et al. 2017 [30]	EPLBD alone	42	95.2 %	100.0 %	21.4 %	11.9 %	7.1 %
	EPLBD with EST	44	97.7 %	100.0 %	13.6 %	13.6 %	11.4 %
Park et al. 2019 [31]	EPLBD alone	100	77 %	92 %	6.5 %	6 %	1 %
	EPLBD with EST	100	78 %	88 %	9.1 %	4 %	3 %
Our study	EPLBD alone	86	90.7 %	100.0 %	30.2 %[2]	9.3 %	4.7 %
	EST	85	77.6 %	95.3 %	48.2 %	9.4 %	5.9 %

EML, endoscopic mechanical lithotripsy; PEP, post-ERCP pancreatitis.
[1] Randomized to EPLBD with removal by a basket or balloon catheter vs. EST with EML.
[2] $P<0.05$
[3] Cholangitis developed after EST alone in 13.3 % ($P=0.026$).
[4] Calculated by the difference between complete stone removal with and without EML.
[5] EST crossover to EPLBD within the index endoscopic retrograde cholangiography.

icant increase in cholangitis. In our study, the incidence of PEP was similar (4.7 % in the EPLBD group and 5.9 % in the EST group), and no severe PEP was observed.

Another explanation for the low rate of PEP is the wide opening of the biliary orifice after EPLBD compared with that after EPBD. As described in long-duration EPBD [33], the adequate opening after EPLBD may avoid edema at the pancreatic orifice and reduce the risk of PEP. In EPBD or EPLBD without EST, the sphincter of Oddi is only dilated and loosened, and edema with hemorrhage and inflammation can develop around the sphincter. After a short-duration EPBD, it is suggested the limited volume expansion around the sphincter causes compression of the pancreatic duct, like a compartment syndrome, which in turn causes PEP. Meanwhile, EPLBD or a long-duration EPBD opens up the sphincter enough and reduces PEP compared with the limited opening during a short-duration EPBD. A recent study showed a balloon dilation time of 30 seconds for minor EST with EPLBD or EPBD reduced the frequency of PEP [34], but the optimal duration of balloon dilation in EPLBD without EST remains unclear.

Cost is also an issue in the management of large CBD stones. In addition to the number of endoscopic procedures, the use of multiple devices poses additional costs. A wide opening after EPLBD can potentially allow stone extraction using a balloon or basket catheter without EML. In the three previous studies [26, 28, 29], EML was used less frequently after EPLBD. In our study, the rate of EML use was relatively high but was lower in the EPLBD group, although the cost was not significantly different:

$1442 in the EPLBD group vs. $1661 in the EST group ($P$ = 0.12). This is probably because the rate of EML use was relatively high in our studies (▶ **Table 5**).

EPLBD can be performed either with a preceding EST or not. While full-length EST was reported to be a risk factor for hemorrhage after EPLBD in a multicenter study [18], there has been a concern about the safety of EPLBD without EST, including the risk of PEP. In the previous RCTs [25, 30, 31], preceding EST did not affect either stone removal or adverse events. The advantages of EPLBD without EST are the simple nature of the procedure and its cost. In patients with a periampullary diverticulum, with surgically altered anatomy, or who are on antithrombotic agents, EPLBD without EST could be a first-line treatment for large CBD stones.

There are some limitations to this study. First, the ampullary interventions were not blinded to the endoscopists, which could potentially affect the single-session complete stone removal rate; however, we limited the procedure time to up to about 1 hour in both groups. In addition, the definition of a large CBD stone varies among clinical trials. We defined large stones as being ≥ 10 mm, but the advantage of EPLBD without EST was more prominent in CBDs ≥ 15 mm according to our study results.

Second, we only enrolled patients ≥ 60 years old because of the lack of data on the long-term outcomes after EPLBD without EST, which limits the generalizability of this study. An analysis of the long-term outcomes in our study will be conducted from biliary interventions after 5 years. EPLBD without EST can potentially preserve the sphincter function when compared to EST. Preserved sphincter function after EPBD is associated with fewer late biliary events compared with EST. When the long-term outcomes of EPLBD were compared to EST or EPBD, EPLBD was comparable to EST [35] but inferior to EPBD [36], suggesting limited preservation of sphincter function after EPLBD. In fact, one study [30] showed sphincter function was lost on manometry 1 week after EPLBD, regardless of preceding EST. Given these limitations in the current evidence, the selection of EPLBD without EST should be considered in the context of short-term outcomes (efficacy of stone removal and safety) and long-term outcomes should be further evaluated.

Finally, our sample size might be too small to detect differences in the clinical outcomes, such as total procedure time and stone extraction time, between EPLBD alone and EST. We assumed a 20 % difference in stone removal for our sample size calculation, with an assumed stone removal rate of 70 % with EST; however, most studies showed that rates of stone removal with EST were above 70 %, and there may be debate about our assumption for sample size calculation.

We also need to comment on negative clinical outcomes, such as total procedure time and stone clearance time. Because we demonstrated a high single-session stone removal rate, with a lesser need to use EML in the EPLBD without EST group, the procedure time would be expected to be short. Although the small sample size of our study was probably a cause of this discrepancy, there is a risk of bias as our study was a single-blind study. A further large-scale study should be conducted to confirm our study results.

In summary, EPLBD without EST compared with EST achieved a significantly higher rate of complete stone removal in a single session, without increasing adverse events. Long-term outcomes, such as recurrent CBD stones, should be evaluated in the future.

Competing interests

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References

[1] Cotton PB, Geenen JE, Sherman S et al. Endoscopic sphincterotomy for stones by experts is safe, even in younger patients with normal ducts. Ann Surg 1998; 227: 201–204

[2] Staritz M, Ewe K, Meyer zum Buschenfelde KH. Endoscopic papillary dilation (EPD) for the treatment of common bile duct stones and papillary stenosis. Endoscopy 1983; 15: (Suppl. 01): 197–198

[3] Komatsu Y, Kawabe T, Toda N et al. Endoscopic papillary balloon dilation for the management of common bile duct stones: experience of 226 cases. Endoscopy 1998; 30: 12–17

[4] Tsujino T, Kawabe T, Komatsu Y et al. Endoscopic papillary balloon dilation for bile duct stone: immediate and long-term outcomes in 1000 patients. Clin Gastroenterol Hepatol 2007; 5: 130–137

[5] Fujita N, Maguchi H, Komatsu Y et al. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: A prospective randomized controlled multicenter trial. Gastrointest Endosc 2003; 57: 151–155

[6] Vlavianos P, Chopra K, Mandalia S et al. Endoscopic balloon dilatation versus endoscopic sphincterotomy for the removal of bile duct stones: a prospective randomised trial. Gut 2003; 52: 1165–1169

[7] Disario JA, Freeman ML, Bjorkman DJ et al. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. Gastroenterology 2004; 127: 1291–1299

[8] Kawabe T, Komatsu Y, Tada M et al. Endoscopic papillary balloon dilation in cirrhotic patients: removal of common bile duct stones without sphincterotomy. Endoscopy 1996; 28: 694–698

[9] Park DH, Kim M-H, Lee SK et al. Endoscopic sphincterotomy vs. endoscopic papillary balloon dilation for choledocholithiasis in patients with liver cirrhosis and coagulopathy. Gastrointestinal Endoscopy 2004; 60: 180–185

[10] Sasahira N, Tada M, Yoshida H et al. Extrahepatic biliary obstruction after percutaneous tumour ablation for hepatocellular carcinoma: aetiology and successful treatment with endoscopic papillary balloon dilatation. Gut 2005; 54: 698–702

[11] Takahara N, Isayama H, Sasaki T et al. Endoscopic papillary balloon dilation for bile duct stones in patients on hemodialysis. J Gastroenterol 2012; 47: 918–923

[12] Yasuda I, Tomita E, Enya M et al. Can endoscopic papillary balloon dilation really preserve sphincter of Oddi function? Gut 2001; 49: 686–691

[13] Isayama H, Komatsu Y, Inoue Y et al. Preserved function of the Oddi sphincter after endoscopic papillary balloon dilation. Hepatogastroenterology 2003; 50: 1787–1791

[14] Kogure H, Tsujino T, Isayama H et al. Short- and long-term outcomes of endoscopic papillary large balloon dilation with or without sphincterotomy for removal of large bile duct stones. Scand J Gastroenterol 2014; 49: 121–128

[15] Kim TH, Kim JH, Seo DW et al. International consensus guidelines for endoscopic papillary large-balloon dilation. Gastrointest Endosc 2016; 83: 37–47

[16] Doshi B, Yasuda I, Ryozawa S et al. Current endoscopic strategies for managing large bile duct stones. Dig Endosc 2018; 30: (Suppl. 01): 59–66

[17] Itoi T, Ryozawa S, Katanuma A et al. Japan Gastroenterological Endoscopy Society guidelines for endoscopic papillary large balloon dilation. Dig Endosc 2018; 30: 293–309

[18] Park SJ, Kim JH, Hwang JC et al. Factors predictive of adverse events following endoscopic papillary large balloon dilation: results from a multicenter series. Dig Dis Sci 2013; 58: 1100–1109

[19] Okuno M, Iwashita T, Yoshida K et al. Significance of endoscopic sphincterotomy preceding endoscopic papillary large balloon dilation in the management of bile duct stones. Dig Dis Sci 2016; 61: 597–602

[20] Ikarashi S, Katanuma A, Kin T et al. Factors associated with delayed hemorrhage after endoscopic sphincterotomy: Japanese large single-center experience. J Gastroenterol 2017; 52: 1258–1265

[21] Cotton PB, Eisen GM, Aabakken L et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010; 71: 446–454

[22] Heo JH, Kang DH, Jung HJ et al. Endoscopic sphincterotomy plus large-balloon dilation versus endoscopic sphincterotomy for removal of bile-duct stones. Gastrointest Endosc 2007; 66: 720–726

[23] Stefanidis G, Viazis N, Pleskow D et al. Large balloon dilation vs. mechanical lithotripsy for the management of large bile duct stones: a prospective randomized study. Am J Gastroenterol 2011; 106: 278–285

[24] Oh MJ, Kim TN. Prospective comparative study of endoscopic papillary large balloon dilation and endoscopic sphincterotomy for removal of large bile duct stones in patients above 45 years of age. Scand J Gastroenterol 2012; 47: 1071–1077

[25] Hwang JC, Kim JH, Lim SG et al. Endoscopic large-balloon dilation alone versus endoscopic sphincterotomy plus large-balloon dilation for the treatment of large bile duct stones. BMC Gastroenterol 2013; 13: 15

[26] Teoh AY, Cheung FK, Hu B et al. Randomized trial of endoscopic sphincterotomy with balloon dilation versus endoscopic sphincterotomy alone for removal of bile duct stones. Gastroenterology 2013; 144: 341–345

[27] Guo Y, Lei S, Gong W et al. A preliminary comparison of endoscopic sphincterotomy, endoscopic papillary large balloon dilation, and combination of the two in endoscopic choledocholithiasis treatment. Med Sci Monit 2015; 21: 2607–2612

[28] Karsenti D, Coron E, Vanbiervliet G et al. Complete endoscopic sphincterotomy with vs. without large-balloon dilation for the removal of large bile duct stones: randomized multicenter study. Endoscopy 2017; 49: 968–976

[29] Omar MA, Abdelshafy M, Ahmed MY et al. Endoscopic papillary large balloon dilation versus endoscopic sphincterotomy for retrieval of large choledocholithiasis: a prospective randomized trial. J Laparoendosc Adv Surg Tech A 2017; 27: 704–709

[30] Cheon YK, Lee TY, Kim SN et al. Impact of endoscopic papillary large-balloon dilation on sphincter of Oddi function: a prospective randomized study. Gastrointest Endosc 2017; 85: 782–790

[31] Park JS, Jeong S, Lee DK et al. Comparison of endoscopic papillary large balloon dilation with or without endoscopic sphincterotomy for the treatment of large bile duct stones. Endoscopy 2019; 51: 125–132

[32] Nakai Y, Isayama H, Sasahira N et al. Risk factors for post-ERCP pancreatitis in wire-guided cannulation for therapeutic biliary ERCP. Gastrointest Endosc 2015; 81: 119–126

[33] Liao WC, Tu YK, Wu MS et al. Balloon dilation with adequate duration is safer than sphincterotomy for extracting bile duct stones: a systematic review and meta-analyses. Clin Gastroenterol Hepatol 2012; 10: 1101–1109

[34] Meng W, Leung JW, Zhang K et al. Optimal dilation time for combined small endoscopic sphincterotomy and balloon dilation for common bile duct stones: a multicentre, single-blinded, randomised controlled trial. Lancet Gastroenterol Hepatol 2019; 4: 425–434

[35] Maruta A, Iwashita T, Uemura S et al. Comparison of late adverse events after endoscopic sphincterotomy versus endoscopic papillary large balloon dilation for common bile duct stones: A propensity score-based cohort analysis. Dig Endosc 2018; 30: 493–500

[36] Hakuta R, Kawahata S, Kogure H et al. Endoscopic papillary large balloon dilation and endoscopic papillary balloon dilation both without sphincterotomy for removal of large bile duct stones: A propensity-matched analysis. Dig Endosc 2019; 31: 59–68