

## Endoscopic papillary large balloon dilation vs endoscopic sphincterotomy for retrieval of common bile duct stones: A meta-analysis

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### Abstract

**AIM:** To compare the efficacy and safety of endoscopic papillary large balloon dilation (EPLBD) with endoscopic sphincterotomy (EST) in retrieval of common bile duct stones ( $\geq 10$  mm).

**METHODS:** PubMed, Web of Knowledge, EBSCO, the Cochrane Library, and EMBASE were searched for

eligible studies. Randomized controlled trials (RCTs) that compared EPLBD with EST were identified. Data extraction and quality assessment were performed by two independent reviewers using the same criteria. Any disagreement was discussed with a third reviewer until a final consensus was reached. Pooled outcomes of complete bile duct stone clearance, stone clearance in one session, requirement for mechanical lithotripsy, and overall complication rate were determined using relative risk and 95%CI. The separate post-endoscopic retrograde cholangiopancreatography complications were pooled and determined with the Peto odds ratio and 95%CI because of the small number of events. Heterogeneity was evaluated with the chi-squared test with  $P \leq 0.1$  and  $I^2$  with a cutoff of  $\geq 50\%$ . A fixed effects model was used primarily. A random effects model was applied when significant heterogeneity was detected. Sensitivity analysis was applied to explore the potential bias.

**RESULTS:** Five randomized controlled trials with 621 participants were included. EPLBD compared with EST had similar outcomes with regard to complete stone removal rate (93.7% vs 92.5%,  $P = 0.54$ ) and complete duct clearance in one session (82.2% vs 77.7%,  $P = 0.17$ ). Mechanical lithotripsy was performed less in EPLBD in the retrieval of whole stones (15.5% vs 25.2%,  $P = 0.003$ ), as well as in the stratified subgroup of stones larger than 15 mm (24.2% vs 40%,  $P = 0.001$ ). There was no statistically significant difference in the incidence of overall adverse events (7.9% vs 10.7%,  $P = 0.25$ ), post-ERCP pancreatitis (4.0% vs 5.0%,  $P = 0.54$ ), hemorrhage (1.7% vs 2.8%,  $P = 0.32$ ), perforation (0.3% vs 0.9%,  $P = 0.35$ ) or acute cholangitis (1.3% vs 1.3%,  $P = 0.92$ ).

**CONCLUSION:** EPLBD could be advocated as an alternative to EST in the retrieval of large common bile duct stones.

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**Key words:** Endoscopic papillary large balloon dilation; Endoscopic sphincterotomy; Mechanical lithotripsy; Common bile duct stones; Meta analysis

**Core tip:** Endoscopic papillary large balloon dilation (EPLBD) was as effective as endoscopic sphincterotomy in large common bile duct stone clearance. However, it had less requirement for endoscopic mechanical lithotripsy, even in stones larger than 15 mm. Besides, EPLBD could be conducted with limited or without precutting of the papilla which may be promising for application in patients with coagulopathy or with surgically modified anatomy. Further investigations are required to confirm this claim.

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## INTRODUCTION

Per-oral endoscopy has been widely accepted as the first-line treatment in removal of common bile duct (CBD) stones, and has gradually replaced conventional surgery. Endoscopic sphincterotomy (EST), as the most commonly used technique, was first introduced in 1974<sup>[1]</sup>. It involved a maximal papillotomy, which not only accounted for 8%-12% of acute adverse events like hemorrhage, perforation<sup>[2]</sup>, but also for long term adverse events like sphincter dysfunction. Endoscopic papillary balloon dilation, introduced as an alternative to EST by Staritz *et al.*<sup>[3]</sup>, could lower the risk of bleeding and perforation, but might result in higher risk of post-procedure pancreatitis<sup>[4-6]</sup>. Furthermore, it could only be applied in removing small to moderate sized stones ( $\leq 10$  mm)<sup>[6]</sup>. Approximately 10%-15% of stones could not be removed by either of the above-mentioned techniques, most of which occurred with stones larger than 10-15 mm<sup>[7]</sup>. In addition, difficult stones (larger than 15 mm, and multiple, barrel-shaped and impacted stones), challenging access to papilla (periampullary diverticulum or postoperative variation), and tortuosity and tapering of the distal common bile duct<sup>[8,9]</sup> increased the failure rate of stone retrieval.

In 2003, Ersoz *et al.*<sup>[10]</sup> recommended a modification of endoscopic papillary balloon dilation which combined large balloon dilation (15-20 mm) with a limited precut of the papilla. It was designed with the aim of reducing adverse events by avoiding a full incision, shortening the procedure time, reducing the use of endoscopic mechanical lithotripsy (EML) and minimizing the adverse events associated with EML<sup>[11]</sup>. However, it has not been

fully accepted by all endoscopists on account of its potential adverse events. A recent meta-analysis revealed that EST plus large balloon dilation was an effective and safe technique based on the pooled rate of clearance at index endoscopic retrograde cholangiopancreatography (ERCP) (89%), related pancreatitis (2.7%), and bleeding (1.06%)<sup>[12,13]</sup>. Some published studies had made a comparison of endoscopic papillary large balloon dilation (EPLBD) with EST for extraction of CBD stones, and the outcomes varied among different institutions<sup>[14-21]</sup>. Thus, it remains controversial whether EPLBD is superior to EST in the retrieval of stones from the CBD, especially large and difficult stones. We performed the present meta-analysis to assess the efficacy and safety of EPLBD by comparing it with EST in patients whose bile duct stones were larger than 10 mm.

## MATERIALS AND METHODS

### Literature search

First, a literature search was performed in electronic databases including PubMed, Web of Knowledge, EBSCO, the Cochrane Library, and EMBASE up to July 2013. Then, Digestive Disease Week and European Gastroenterology Week meetings were scanned for relevant meeting abstracts. References cited in all retrieved articles were also reviewed for additional articles. The search terms used were “catheterization”, “endoscopic papillary large balloon dilation”, “balloon dilation”, “balloon catheter”, “endoscopic sphincterotomy”, “vater papillotomy”, “sphincterotomy”, “biliary sphincterotomy”, “gallstone”, “common bile duct stone”, “common bile duct calculi”, “choledocholithiasis”. All the above were combined with “AND” or “OR”.

### Study selection

Randomized controlled trials with a full text available that compared the efficacy and safety of EPLBD and EST in the removal of common bile duct stones ( $\geq 10$  mm) were included for further meta-analysis.

### Data extraction

Data extraction was performed independently by two reviewers (Mei M and Xu ZQ). Both used the same form for extracting relevant data as follows: baseline trial data (*e.g.*, first author, publication year, article type, number of subjects, sex ratio, intervention, number of stones, mean diameter of stones, balloon size in EPLBD, extent of the sphincterotomy in EPLBD); complete stone removal rate; duct clearance in one session; the requirement for mechanical lithotripsy; the adverse events rate (pancreatitis, perforation, bleeding and acute cholangitis)<sup>[22]</sup>. A third reviewer (Jin PP) joined the discussion to make the final judgment in cases of disagreement.

### Quality assessment

The Jadad score<sup>[23]</sup> was applied to assess the quality of the randomized trials by two investigators (Jin PP and Sun

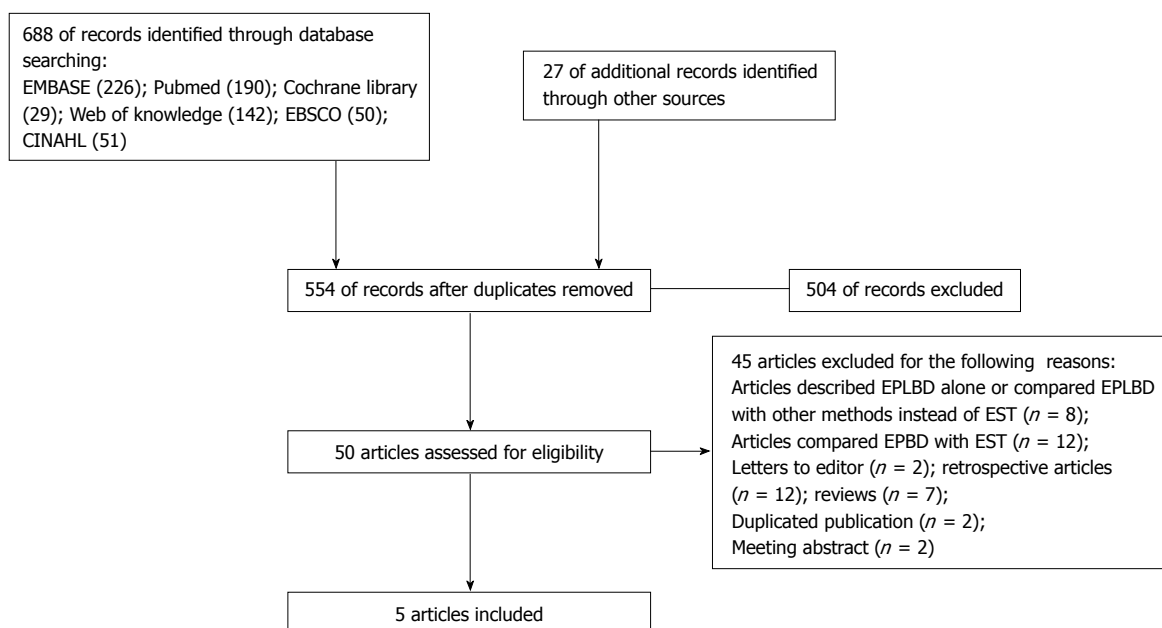


Figure 1 Flow diagram of study selection.

LM). The quality was ranked according to three aspects: randomization, double-blindness and description of withdrawals or dropouts. The final score ranged from 0 to 5: a score lower than 2 indicated lower quality whereas studies achieving a score higher than 3 were considered high quality. Again, if disputes arose, resolution would be made after discussion with a third reviewer (Mei M).

### Statistical analysis

Data analysis was conducted with Review Manager (Version 5.1, Cochrane Collaboration, Oxford, United Kingdom). The primary outcome was the efficacy of each procedure, including complete stone removal rate, and stone clearance in the first ERCP session. The secondary outcomes were overall requirement for mechanical lithotripsy, the overall post-ERCP adverse event rate, and incidences of pancreatitis, hemorrhage, acute cholangitis and perforation. Comparisons of pooled effects of complete stone removal rate, stone clearance in the first ERCP session, requirement for mechanical lithotripsy, and overall adverse event rate were described by the RR and 95%CI. While separate post-ERCP adverse events were pooled and compared using the Peto OR, because of the small number of events. A statistically significant difference was defined as  $P < 0.05$ . Heterogeneity among studies was assessed by the  $\chi^2$  test with  $P \leq 0.1$  and calculating  $I^2$  with a cutoff of  $\geq 50\%$ <sup>[24]</sup>. A fixed effects model was primarily used, and a random effects model was applied when a significant heterogeneity was detected.

Sensitivity analysis was conducted to examine the stability of the original pooled outcomes. First, it was carried out by reanalyzing data using another statistical effects model (e.g., switching from the fixed effects model to the random effects model). Then, sensitivity analysis was performed by excluding the study of Oh and Kim,

in which EPLBD was conducted without pre-sphincterotomy<sup>[16]</sup>. If the exclusion of this study did not cause substantial variation from the primary outcome, the study would be kept in the final analyses.

Subgroup analysis was performed to explore the requirement of EML in management of CBD stones whose diameter were larger than 15 mm.

## RESULTS

### Study selection and quality assessment

The search of the above-mentioned database yielded 715 articles, and 161 articles were excluded because of duplication. Among the 554 included articles, 504 were further excluded for the following reasons: a review, case series or irrelevant articles, and 50 were potentially included for full text review. Finally, 5 randomized controlled trials (RCTs)<sup>[14-16,25,26]</sup> with 621 subjects met the inclusion criteria and were selected for evaluation and analysis. The detailed procedure of literature searching is shown in Figure 1. The baseline characteristics of all articles were listed in Table 1. The quality of the 5 RCTs was assessed with the Jadad score. As shown in Table 2, all included studies had a final score  $\geq 3$  and were of high quality.

### Data analysis of efficacy and safety

**Complete stone removal rate and complete duct clearance in one session:** All 5 RCTs had reported a comparison of the outcomes of EPLBD and EST as complete stone removal rate and complete duct clearance in one session. Only one trial by Qian *et al.*<sup>[25]</sup> reported significant superiority of EPLBD in the first session for complete duct clearance (80.9% *vs* 60.8%,  $P = 0.046$ ). While no heterogeneity was found in our meta-analysis in either of the aspects above, a fixed effects model was

**Table 1** Baseline characteristics of the included studies

Ref.	Sex (male/female)		Intervention	Mean diameter of stones (mm)		Mean number of CBD stones		Balloon size (mm) in EPLBD	Extent of sphincterotomy in EPLBD
	Group 1	Group 2		Group 1	Group 2	Group 1	Group 2		
Qian <i>et al</i> <sup>[25]</sup> , 2013	32/31	36/33	Group 1 small EST plus EPLBD ( <i>n</i> = 63)	20.6 ± 5.4	20.3 ± 5.3	2.2 ± 1.2	2.3 ± 1.3	12-20	Limited to one-third that in the minor EST group
Teoh <i>et al</i> <sup>[26]</sup> , 2012	32/41	40/38	Group 2 conventional EST ( <i>n</i> = 69)	12.47	13.26	≥ 1	≥ 1	≤ 15	One third to one half of the size of papilla
			Group 1 limited EST plus EPLBD ( <i>n</i> = 73)						
Oh <i>et al</i> <sup>[16]</sup> , 2012	20/20	23/20	Group 2 complete EST ( <i>n</i> = 78)	13.2 ± 3.6	13.1 ± 3.9	NA	NA	10-18	No precut
			Group 1 EPLBD alone ( <i>n</i> = 40)						
Kim <i>et al</i> <sup>[15]</sup> , 2009	NA	NA	Group 2 EST ( <i>n</i> = 43)	20.8 ± 4.1	21.3 ± 5.2	2.2 ± 1.3	2.3 ± 1.2	15-18	Mid-portion of papilla
			Group 1 small EST plus ELPBD ( <i>n</i> = 27)						
Heo <i>et al</i> <sup>[14]</sup> , 2007	48/52	50/50	Group 2 EST alone ( <i>n</i> = 28)	16.0 ± 0.7	15.0 ± 0.7	2.7 ± 2.7	2.2 ± 1.9	12-20	A third of the size of EST group
			Group 1 EST plus EPLBD ( <i>n</i> = 100)						
			Group 2 EST alone ( <i>n</i> = 100)						

EPLBD: Endoscopic papillary large balloon dilation; EST: Endoscopic sphincterotomy; CBD: Common bile duct; NA: Not available.

**Table 2** Quality assessment of the included articles based on the Jadad score

Ref.	Jadad score of RCTs			Article type	Score
	Randomization	Blindness	Withdrawal		
Qian <i>et al</i> <sup>[25]</sup> , 2013	Appropriate	NA	Clear	Full text	3
Teoh <i>et al</i> <sup>[26]</sup> , 2012	Appropriate	Double	Clear	Full text	5
Oh <i>et al</i> <sup>[16]</sup> , 2012	Appropriate	Single	Clear	Full text	4
Kim <i>et al</i> <sup>[15]</sup> , 2009	Appropriate	NA	Clear	Full text	3
Heo <i>et al</i> <sup>[14]</sup> , 2007	Appropriate	NA	Clear	Full text	3

RCT: Randomized controlled trial.

applied. The pooled outcomes demonstrated similar efficacy of EPLBD and EST in complete CBD stone clearance (93.7% *vs* 92.5%, *P* = 0.54) and complete duct clearance in one session (82.2% *vs* 77.7%, *P* = 0.17), as shown in Table 3.

**Requirement for mechanical lithotripsy:** All the included articles provided data on the use of EML. Two articles<sup>[25,26]</sup> mentioned the difference between EPLBD and EST (*P* < 0.05). The pooled outcome of the current analysis implied that EPLBD might reduce the need for EML when compared with EST in the management of CBD stones (15.5% *vs* 25.2%, *P* = 0.003) (See Figure 2A). No heterogeneity was detected.

**Overall adverse events:** Adverse events overall included procedure-related pancreatitis, hemorrhage, perforation, acute cholangitis and cholecystitis. Morbidities in the 5 RCTs were all defined and graded according to the modified 1991 Cotton consensus<sup>[22]</sup>. One trial<sup>[15]</sup> mentioned that no adverse events occurred with either EPLBD or EST (0/27 *vs* 0/28). In the light of the pooled RR of our current meta-analysis (RR = 0.75; 95%CI: 0.46-1.22), the overall adverse event rates showed similar rates for EPLBD compared with EST. This conclusion was consistent with that in each article included.

**Analysis of the separate postoperative adverse events:** Procedure-related pancreatitis was defined as epigastric pain for more than 24 h duration with at least a 3-fold elevation in serum amylase and/or lipase concentration. Hemorrhage was defined as a decrease in hemoglobin concentration of > 2 g/dL or clinical manifestation of bleeding (not only endoscopic) after the procedure, such as melena or hematemesis<sup>[22]</sup>. Cholangitis was considered when the temperature was above 38 °C and accompanied by right upper quadrant pain<sup>[22]</sup>. Given the rare incidence of these adverse events, the Peto OR method was used. No statistically significant difference was found in terms of post-ERCP pancreatitis (Peto OR = 0.79; 95%CI: 0.37-1.68), hemorrhage (Peto OR = 0.57; 95%CI: 0.19-1.71), cholangitis (Peto OR = 1.08; 95%CI: 0.27-4.37) or perforation (Peto OR = 0.39; 95%CI: 0.06-2.81) for EPLBD compared with EST, as shown in Table 3.

### Sensitivity analysis

Final conclusions were not altered when the results were reanalyzed by the random effects model. Moreover, both primary and secondary outcomes showed no substantial change after we eliminated the trial by Oh and Kim<sup>[16]</sup>. Only the heterogeneity of complete duct clearance in one session increased (*I*<sup>2</sup> = 58%, *P* = 0.07), so we had to use

**Table 3** Pooled effects of efficacy and safety in randomized controlled trials *n* (%)

Items	Incidence of		Number of subjects	Heterogeneity $I^2$ (P)	Analysis model	Test for overall effect		RR/Peto OR (95%CI)
	EPLBD ( <i>n</i> = 303)	EST ( <i>n</i> = 318)				Z	P value	
Complete stone removal rate	93.7 (284)	92.5 (294)	621	0% (0.82)	Fixed (M-H)	0.61	0.54	RR = 1.01 (0.97-1.06)
Complete ductal clearance in one session	82.2 (249)	77.7 (247)	621	44% (0.13)	Fixed (M-H)	1.36	0.17	RR = 1.06 (0.98-1.14)
Requirement for EML	15.5 (47)	25.2 (80)	621	10% (0.35)	Fixed (M-H)	2.98	0.003 <sup>a</sup>	RR = 0.62 (0.45-0.85)
Overall Adverse events	7.9 (24)	10.7 (34)	621	0% (0.97)	Fixed (M-H)	1.16	0.25	RR = 0.75 (0.46-1.22)
Post-ERCP pancreatitis	4.0 (12)	5.0 (16)	621	0% (0.98)	Peto	0.62	0.54	Peto OR = 0.79 (0.37-1.68)
Hemorrhage	1.7 (5)	2.8 (9)	621	28% (0.25)	Peto	1.00	0.32	Peto OR = 0.57 (0.19-1.71)
Perforation	0.3 (1)	0.9 (3)	621	34% (0.22)	Peto	0.93	0.35	Peto OR = 0.39 (0.06-2.81)
Acute cholangitis	1.3 (4)	1.3 (4)	621	0% (0.71)	Peto	0.11	0.92	Peto OR = 1.08 (0.27-4.37)

<sup>a</sup>Significant difference. EML: Endoscopic mechanical lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography; Fix: Fixed effects model; M-H: Mantel-Haenszel.

the random effects model, as shown in Table 4.

### Subgroup analysis

Four RCTs reported the need for EML in retrieval of large sized stones ( $\geq 15$  mm). The heterogeneity was acceptable with  $\chi^2 = 3.74$ ,  $I^2 = 20\%$ , and  $P = 0.29$ . The fixed effects model of the pooled outcome (24.2% *vs* 40%,  $P = 0.001$ ) revealed that EPLBD was superior to EST in reducing the use of EML for large stones as shown in Figure 2B.

## DISCUSSION

EPLBD is an effective and safe approach for the extraction of large CBD stones ( $\geq 10$  mm). It facilitates stone removal, but not at the expense of increased pancreatitis, hemorrhage and use of EML.

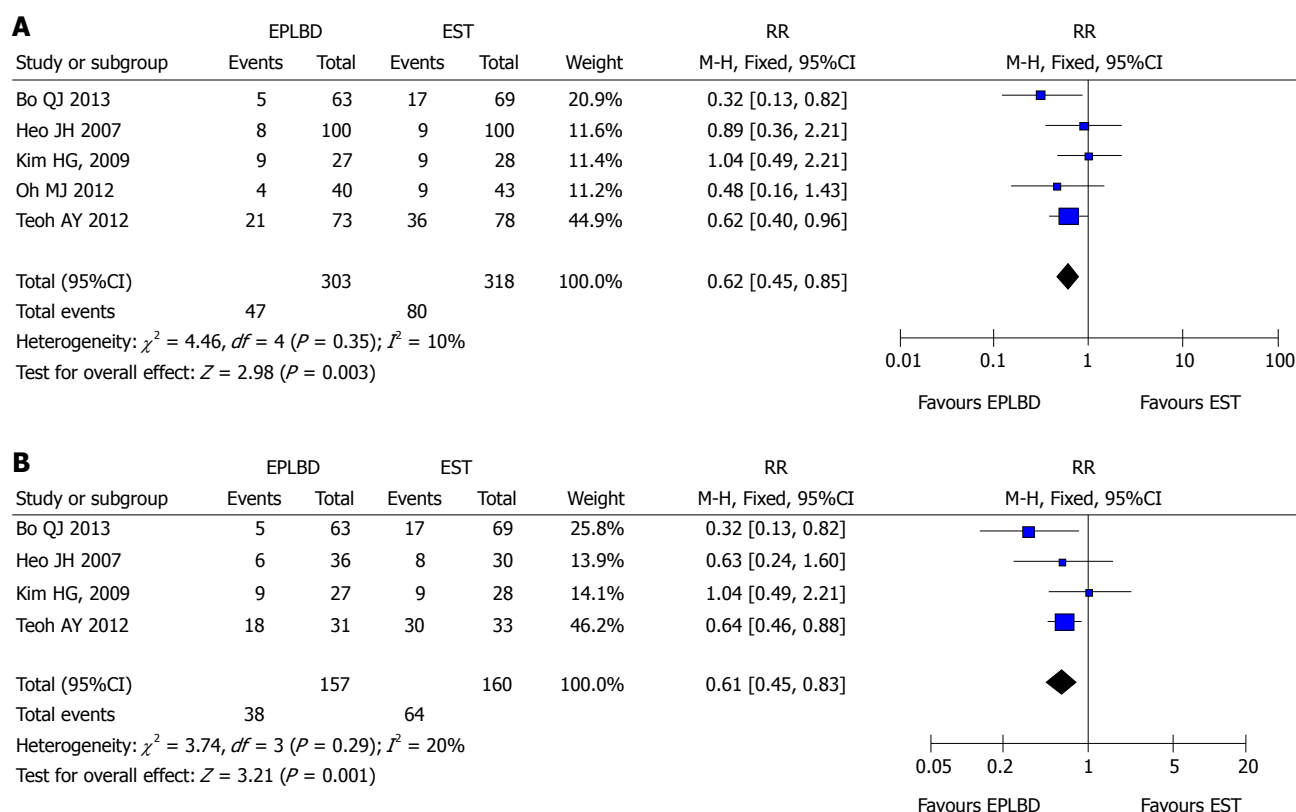
In previous retrospective articles, EPLBD was reported to be more efficient than EST in initial CBD stone clearance ( $P < 0.05$ )<sup>[18,19,21]</sup>, while our current meta-analysis of RCTs suggested that EPLBD achieved equivalent success to EST both for complete stone removal or stone clearance in the first session. It was consistent with a former meta-analysis by Feng *et al*<sup>[27]</sup>, but in contrast with the meta-analysis of 6 retrospective articles by Liu *et al*<sup>[28]</sup>. The reason for this discrepancy is possibly related to study design including sample size, the extent of EST, the size or shape of the stone or CBD, the papillary balloon and the operator's personal experience.

EML might be performed less in EPLBD than EST based on our pooled outcome. EML is generally used in cases of failed stone removal using the Dormia basket. However, disadvantages such as lengthy procedure time, possible injury of the EST site or CBD as a result of using accessories, and impaction of the stone-capturing basket<sup>[11]</sup> hampered its wide application. Stefanidis *et al*<sup>[29]</sup>

compared EPLBD plus EST with EML plus EST in a RCT, where similar efficacy was found but there was a higher frequency of adverse events in the latter. This raised the question whether EPLBD could reduce the use of EML. Though a few of the studies<sup>[18-21,25,26,30]</sup> tried to explore this, no definite consensus has been reached up to now. Even in 2 previous meta-analyses, different outcomes were achieved. The need for EML in our review was significantly reduced with EPLBD compared to EST. The same conclusion was also made for large stones ( $\geq 15$  mm). The possible explanation was that a large diameter balloon could tear the sphincter and offer a more adequate orifice for removal of large stones<sup>[27]</sup>. However, the requirement for EML might depend on stone size, the extent of EST, the shape of stones and the bile duct<sup>[14]</sup>. Therefore, EML could still be applied when large balloon dilation by itself could not stretch the distal bile duct wall enough to be effective for removal of large stones<sup>[15]</sup>.

Regarding safety, our meta-analysis suggested that EPLBD did not increase the frequency of overall adverse events, or any single one.

To our knowledge, the common maximum balloon diameter adopted in EPBD was 10 mm. In EPLBD, the balloon was enlarged to 12 to 20 mm or more, which resulted in a major concern of pancreatitis. The balloon size in our included RCTs ranged from 10 to 20 mm as shown in Table 1. However, there was no increase in pancreatitis observed (EPLBD *vs* EST, 4.0% *vs* 5.0%,  $P = 0.54$ ). One explanation might be that a prior EST helps to separate the pancreatic orifice from the biliary orifice and guide the orientation of the dilated balloon towards the CBD, thus preventing pressure overload on the main pancreatic duct<sup>[18,20]</sup>. The other possible reason may be the longstanding CBD stones which lead to the dilation of CBD and make the papillary orifice persistently open<sup>[16]</sup>. In addition, the inflation time in the 5 full



**Figure 2 Forest plot of risk ratio and 95%CI.** A: Efficiency of endoscopic mechanical lithotripsy (EML) for overall common bile duct stones; B: Requirement for EML in large common bile duct stones ( $\geq 15$  mm). EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation.

**Table 4 Sensitivity analysis of primary pooled outcome in the randomized controlled trials**

Items	Adjusted pooled outcome of RCTs with article excluded		
	Heterogeneity $I^2$ ( $P$ )	$P$ value	RR or Peto OR (95%CI)
Complete stone removal rate	0% (0.70)	0.63	1.01 (0.97-1.06)
Complete ductal clearance in one session	58% (0.07)	0.37	1.06 (0.93-1.22)
Requirement of EML	27% (0.25)	0.007 <sup>a</sup>	0.64 (0.46-0.89)
Overall adverse events	0% (1.00)	0.24	0.69 (0.37-1.29)
Post-ERCP pancreatitis	0% (0.93)	0.61	0.80 (0.35-1.86)
hemorrhage	35% (0.22)	0.68	0.69 (0.12-4.01)
perforation	0% (0.99)	0.09	0.14 (0.01-1.40)
Acute cholangitis	0% (0.70)	0.72	0.72 (0.12-4.20)

<sup>a</sup>Significant difference ( $P < 0.05$ ). RCT: Randomized controlled trial; EML: Endoscopic mechanical lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography.

texts<sup>[14-16,25,26]</sup> were set around 30-60 s. Pancreatitis may not happen within this time frame. It is speculated that post-procedure pancreatitis might not be associated with larger balloon size, but related more to longer procedure time and a less dilated CBD<sup>[31]</sup>.

Although no statistically significant difference was found, hemorrhage seemed to occur less often in EPLBD (1.7% *vs* 2.8%). It may be attributed to the partial precut before large balloon insertion, which has an advantage

over a major incision for EST, since the possibility of cutting the large vessel in the papillary roof is reduced. Meanwhile, some intra-procedural bleeding can be more easily controlled in the procedure of EST plus EPLBD owing to balloon tamponade of the sphincterotomy site. Furthermore, EPLBD could be performed without prior EST, and large balloon dilation alone had good efficacy and safety for patients with periampullary diverticula and Billroth II gastrectomy<sup>[32-34]</sup>. Therefore, it might be attractive for patients with a bleeding tendency and cirrhosis, as well as for those with anatomical problems. However, further clinical trials are expected to confirm this conclusion.

The most serious adverse event of EPLBD may be perforation and it is more likely to occur in those with a distal CBD stricture<sup>[11,20]</sup>. Thus, appropriate patient selection becomes important. Generally, patients targeted for EPLBD may be those with CBD dilation but without strictures of the distal CBD<sup>[35]</sup>, and the size of the selected balloon should not exceed the maximal diameter of the CBD. The advantage of EPLBD is that endoscopists can directly observe the remaining intact mucosa during gradual balloon inflation after partial EST, which helps to minimize the risk of perforation by avoiding excessive pressure<sup>[35]</sup>. The frequency of cholangitis did not seem to increase after EPLBD. This may due to the wider papillary access achieved with large balloon inflation and effective biliary drainage, both of which contribute to prevent the obstruction of the ampullary orifice and relieve papillary edema.

Long-term complications such as sphincter dysfunction could not be compared in the current meta-analysis, because of the short duration of follow-up in all articles included. However, Lee *et al.*<sup>[11]</sup> had mentioned in his review that EPLBD might not preserve the function of the sphincter of Oddi, but may cause an even worse condition than EST. The pressure gradient between the CBD and the duodenum will probably be eliminated after EPLBD, just as with surgical sphincteroplasty. So far, there has been no relevant RCT or evidence to confirm this claim.

It is important to point out that an operator's proficiency of EPLBD or EST might give rise to a different result of overall stone clearance rate and adverse event rate. Operators with experience of at least 100 procedures were more likely to achieve a safe precut sphincterotomy<sup>[36]</sup>. In our present review, only one article by Heo *et al.*<sup>[14]</sup> referred to the background of endoscopists, with performance of more than 300 biliary interventions per year. Others did not mention or simply mentioned "experienced endoscopists". Thus, the varying personal experience in the 2 techniques may have a potential influence over the outcome of successful stone clearance and adverse event rates.

Several limitations existed in the current meta-analysis. Firstly, the EPLBD group consisted of 2 different surgical methods (EPLBD with pre-cut and EPLBD alone), which likely caused a potential bias. Even though our pooled outcomes showed no substantial changes in the later sensitivity analysis when the trial of EPLBD alone was excluded, whether single EPLBD is similar to EST plus EPLBD needs further investigation. Secondly, EPLBD was first advocated in 2003 and has become popular in recent years, therefore, the number of RCTs comparing EPLBD and EST was limited (less than 10). As a result, a funnel plot could not be performed to test publication bias in the current meta-analysis. Thirdly, the 5 RCTs were mainly carried out in China and South Korea. Thus, relevant research, especially from Western countries is warranted to enhance the reliability of the conclusion. Finally, reports in languages other than English were excluded. The risk of language bias had to be considered, but it may not result in any notable bias in the assessment of interventional effectiveness.

In summary, EPLBD is an excellent option in managing difficult CBD stones. Given the minor incision necessary, the reduced requirement for EML and the low frequency of adverse events, EPLBD may be prospectively applied in patients with complicated papillary anatomy, coagulopathy or those who cannot tolerate EST or endoscopic papillary balloon dilation for any other reasons. Further investigation is required to confirm the current conclusions.

## COMMENTS

### Background

Endoscopic papillary large balloon dilation (EPLBD) is a newly developed technique applied in retrieval of large common bile duct (CBD) stones ( $\geq 10$  mm).

Generally, a balloon with a diameter of 12-20 mm would be used to dilate the CBD after limited pre-cutting of the papilla. It is believed to combine the advantages of endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilation but minimize the complications of both.

### Research frontiers

The comparison of the efficacy and safety of EPLBD and EST showed different outcomes in previous trials. The authors performed a meta-analysis of RCTs to explore whether EPLBD is comparable or superior to EST in the extraction of CBD stones.

### Innovations and breakthroughs

In the current review, the pooled outcome of 5 RCTs showed that EPLBD was as efficient as EST in stone removal. Although the balloon in EPLBD was enlarged, the frequency of post-ERCP pancreatitis was not increased. The incidences of hemorrhage, perforation and cholangitis after EPLBD were similar to those after EST. Most importantly, there was a lower need for endoscopic mechanical lithotripsy (EML), even in the retrieval of stones larger than 15 mm. This is the first meta-analysis to compare EPLBD with EST based on RCTs. Therefore, it is meaningful, reliable and has high quality.

### Applications

EPLBD is suggested as an alternative to EST in the extraction of large or difficult CBD stones. When compared with EST, EPLBD appears safe and effective and also decreases the need for EML. In addition, EPLBD could be performed without pre-cutting the papilla, which may be attractive for patients with coagulopathy.

### Terminology

Endoscopic papillary balloon dilation: This technique involves dilation of the biliary sphincter with a balloon typically 6-10 mm in diameter followed by stone extraction. Endoscopic sphincterotomy: This is the most commonly used therapy in the removal of CBD stones. It could eliminate the principal anatomic barrier impeding stone passage by cutting the biliary sphincter and facilitating stone extraction. Endoscopic mechanical lithotripsy: This technique is used to break stones into fragments when the diameter of the CBD stone is larger than the papillary sphincter.

### Peer review

The current meta-analysis is a serious scholarly work. The method is painstaking, objective and scientific. The conclusion is trustworthy. It is a valuable study.

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