Thieme

Complete endoscopic sphincterotomy with vs. without large-balloon dilation for the removal of large bile duct stones: randomized multicenter study

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ABSTRACT

Background and study aims Endoscopic sphincterotomy plus large-balloon dilation (ES-LBD) has been reported as an alternative to endoscopic sphincterotomy for the removal of bile duct stones. This multicenter study compared complete endoscopic sphincterotomy with vs. without large-balloon dilation for the removal of large bile duct stones. This is the first randomized multicenter study to evaluate these procedures in patients with exclusively large common bile duct (CBD) stones.

Methods Between 2010 and 2015, 150 patients with one or more common bile duct stones ≥ 13 mm were randomized to two groups: 73 without balloon dilation (conventional group), 77 with balloon dilation (ES-LBD group). Mechanical lithotripsy was subsequently performed only if the stones were too large for removal through the papilla. Endoscopic sphincterotomy was complete in both groups. Patients could switch to ES-LBD if the conventional procedure failed.

Results There was no between-group difference in number and size of stones. CBD stone clearance was achieved in 74.0 % of patients in the conventional group and 96.1 % of patients in the ES-LBD group ($P < 0.001$). Mechanical lithotripsy was needed significantly more often in the conventional group (35.6 % vs. 3.9 %; $P < 0.001$). There was no difference in terms of morbidity (9.3 % in the conventional group vs. 8.1 % in the ES-LBD group; $P = 0.82$). The cost and procedure time were not significantly different between the groups overall, but became significantly higher for patients in the conventional group who underwent mechanical lithotripsy. The conventional procedure failed in 19 patients, 15 of whom underwent a rescue ES-LBD procedure that successfully cleared all stones.

Conclusions Complete endoscopic sphincterotomy with large-balloon dilation for the removal of large CBD stones has similar safety but superior efficiency to conventional treatment, and should be considered as the first-line step in the treatment of large bile duct stones and in rescue treatment.

Trial registered at ClinicalTrials.gov (NCT02592811).

Introduction

Endoscopic sphincterotomy was first described in 1974 yet is still the mainstay of therapy for common bile duct (CBD) stones [1]. However, 10 % of patients have CBD stones that are difficult to extract and require mechanical lithotripsy [2, 3]. As mechanical lithotripsy is not only a technically challenging procedure but also time-consuming and costly, endoscopic sphincterotomy plus large-balloon dilation (ES-LBD) was developed in 2003 as an alternative method [4]. There is recent consensus that this procedure is safe; however, there is an ongoing debate over whether it is superior to the conventional endoscopic treatment of endoscopic sphincterotomy with or without mechanical lithotripsy for CBD stone treatment [5 – 9]. In particular, the technical steps and explicit indications for ES-LBD in the therapeutic strategy for CBD stones are still unclear. For instance, most authors recommend that ES-LBD should involve a "small" endoscopic sphincterotomy with large-balloon dilation in order to decrease procedural morbidity [8 – 14]. Moreover, most relevant randomized studies have included patients with CBD stones of any size [11, 14 – 16], whereas the real medical issue is to determine the optimal adjunctive technique in cases of failed CBD stone extraction after standard endoscopic sphincterotomy. To help resolve this issue, we conducted a large multicenter study to compare ES-LBD with the conventional treatment of endoscopic sphincterotomy with or without mechanical lithotripsy for the extraction of exclusively large CBD stones. This study is the first randomized multicenter study to evaluate ES-LBD in patients with exclusively large CBD stones.

Patients and methods

This prospective, comparative, randomized, multicenter study was conducted in 21 expert endoscopy centers from September 2010 to March 2015. All patients gave written informed consent to all necessary endoscopic procedures.

The study was carried out according to the principles of the Declaration of Helsinki, and the protocol was approved by the Ile-de-France IX ethics committee of University Hospital – Créteil, France (#10-009) and the French national drug safety agency (ANSM; #2009-A01135-52). The trial is registered at ClinicalTrials.gov (NCT02592811) and followed CONSORT guidelines.

All investigators were members of a French taskforce of gastroenterologists working on digestive endoscopy (GRAPHE: Groupe de Réflexion et d'Action des Praticiens Hépatogastroentérologues en Endoscopie Digestive). All authors declare that they had access to the study data and had reviewed and approved the final manuscript.

Patients

Consecutive patients aged ≥ 18 years who were scheduled for endoscopic retrograde cholangiopancreatography (ERCP) for CBD stones were invited to participate. Inclusion was determined during ERCP if the cholangiogram confirmed the presence of one or more CBD stones with a minimal diameter of ≥ 13 mm. Stone size was assessed on the cholangiogram by comparing its smallest and largest diameters against the approximately 13 mm diameter of the duodenoscope. Exclusion criteria were: history of or active acute pancreatitis, distal CBD stricture (defined as a distal CBD tapering of more than 10 mm in length), presence of intrahepatic stones, history of Billroth II or Roux-en-Y reconstruction, coagulation disorders (such as partial thromboplastin time > 42 seconds, prothrombin time [Quick value] < 50 %, platelet count < 50 000/mm³), currently taking clopidogrel, pregnancy, and inability to give informed consent.

Randomization was performed by an independent research assistant using a random number generator. The assignments were edited, sealed in identical opaque envelopes, delivered to the 21 investigators' endoscopy units, and opened locally during the procedure when the patient matched the inclusion criteria on the cholangiogram obtained after effective deep

CBD cannulation. Included patients were randomized into two groups: conventional group – complete endoscopic sphincterotomy, plus mechanical lithotripsy only if necessary for stone extraction; or ES-LBD group – complete endoscopic sphincterotomy systematically followed by large-balloon dilation of the papilla from a diameter of 12 to 20 mm (according to stone diameter), plus mechanical lithotripsy only if necessary.

Patients could be switched via a crossover procedure to ES-LBD if the conventional procedure failed to extract the stones: failure was registered to the conventional procedure, but delay before switching to ES-LBD and the success rate in this rescue situation were also recorded.

ERCP procedure

Both groups

ERCP procedures were performed with patients under general propofol-induced anesthesia and lying on the back or in the left lateral decubitus position. The duodenoscopes used were: Olympus TJF-160VR or TJF-Q180V (Olympus Europe Inc., Hamburg, Germany) at 17 endoscopy units; Fujinon ED-250XT5 (Fujifilm France [Medical Systems], Asnieres, France) at 2 endoscopy units; Pentax ED 3480 TK and ED 3490 TK (Pentax Medical, Argenteuil, France) at 2 endoscopy units. The types of sphincterotome, catheter, guidewire, extraction balloon, and mechanical lithotripsy material used for the procedures were chosen at the discretion of each endoscopist.

In both groups, endoscopic sphincterotomy was complete (i. e. performed on the full length of the transverse fold), and any subsequent mechanical lithotripsy was performed only if stones were deemed too large for removal through the papilla.

Prophylactic antibiotics were given as routine. In the event of perforation or active bleeding during ERCP, the recommended practice was to insert a biliary fully covered stent at the end of the procedure.

ES-LBD group

Every ES-LBD procedure used a 12 – 20 mm diameter wire-guided balloon (HERCULES; Cook Medical, Winston Salem, North Carolina, USA). The balloon diameter was chosen based on the size of the bile duct and diameter of the largest stone. The balloon was gradually filled with diluted contrast medium and remained inflated until the waist of the balloon had disappeared on fluoroscopy.

Data collection and post-ERCP management

Baseline data were collected from the patients before ERCP. Where performed, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and routine laboratory values were obtained before or in the last 24 hours prior to ERCP. EUS was performed immediately before ERCP, usually during the same procedure.

After ERCP, the size of the largest stone (maximal and minimal diameters), diameter of the CBD, number of stones, procedure time, cost of consumables used for ERCP, and use of mechanical lithotripsy were recorded.

Patients remained in hospital for at least 24 hours after the ERCP procedure and were examined to rule out the presence of any perforation, bleeding, or acute pancreatic, septic or other complications. Immediate complications were recorded. Any perforation was suspected from clinical data and confirmed by CT. Any bleeding was classified as severe if more than 4 units of transfused blood was needed, or mild if not. Acute pancreatitis was defined as the presence of abdominal pain and serum lipase greater than three times the normal value. The severity of acute pancreatitis was evaluated by CT and on evolution of clinical data. Septic complications (angiocholitis, cholecystitis or septicemia) were evaluated clinically and with laboratory values, ultrasound or CT images, and bacterial cultures.

Follow-up data (such as pain, vomiting, fever or other complications) were evaluated by clinical examination and laboratory blood tests (liver function tests, lipasemia, creatininemia, blood count, and C-reactive protein), and collected at 1 month post-surgery. Any suspected ERCP complications or recurrence of CBD stones were evaluated by ultrasound, CT or MRI. Patients were considered lost to follow-up if they were unable to attend a clinical examination within 3 months of randomization.

Complications and deaths were recorded for both groups. Morbidities were defined and graded according to the modified 1991 consensus guidelines [17].

Outcome measurements

The primary outcome measure in both groups was the stone clearance rate in one endoscopic session. Secondary outcomes included initial and 1-month morbidities and mortalities, rates of mechanical lithotripsy, procedure time, and procedure costs.

Sample-size calculation and statistical analyses

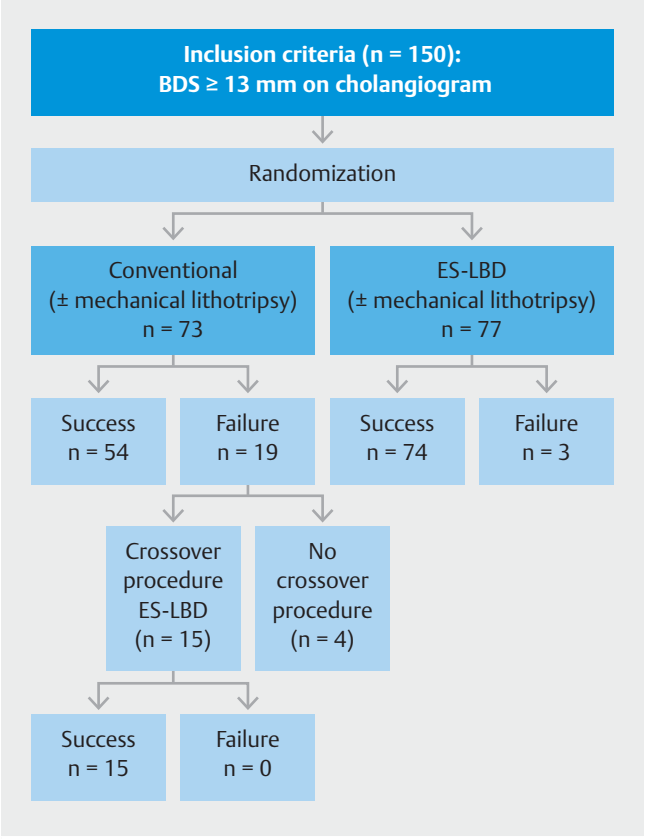
Assuming a 15 % difference in stone clearance rate in one endoscopic session with 80 % in the conventional group and 95 % in the ES-LBD group (based on previous positive series) [11, 13], with a type-I error of 0.05 (2-sided) and a power of 0.8, the study required a total 150 patients (randomized into two groups).

Quantitative variables were expressed as mean (SD) or as median and interquartile range (IQR) when describing time data. Qualitative variables were expressed as numbers and percentages. Continuous variables were compared using a Student's *t* test or Wilcoxon-Mann-Whitney *U* test, as required. Categorical variables were compared using the chi-squared test or Fisher's exact test, as required.

Statistical analyses were performed using Stata 14 software (StataCorp LP, College Station, Texas, USA).

Results

From July 2010 to March 2015, a total of 150 patients were included at 21 centers: 73 patients were randomized to the conventional group and 77 to the ES-LBD group (▶ **Fig. 1**). Five centers included more than 10 patients per center (high-inclusion centers), 8 centers included 5 – 10 patients per center, and 7



▶ **Fig. 1** Flow of patients through the study. Conventional group, complete endoscopic sphincterotomy without balloon dilation; ES-LBD, endoscopic sphincterotomy plus large-balloon dilation.

centers included fewer than 5 patients per center (low-inclusion centers).

There were no between-group differences in patient demographic details, with the exception of age, which was significantly higher in the conventional group compared with the ES-LBD group (▶ **Table 1**). There were no differences in indications for ERCP, number and size of CBD stones, CBD diameter, and rates of periampullary diverticula, cholecystectomy history or prior endoscopic sphincterotomy (▶ **Table 1**). The mean diameter of the dilation balloon used in the ES-LBD group was 16.79 ± 4.7 mm.

Stone clearance rate

The CBD clearance rate was significantly lower in the conventional group (54/73 [74.0 %]) vs. the ES-LBD group (74/77 [96.1 %]; $P < 0.001$) (▶ **Fig. 2**).

The stone clearance rate was not significantly modified by presence (n = 38) or absence (n = 112) of periampullary diverticula either within each group or in the global population: stone clearance rate was 84.8 % in the absence of diverticula vs. 85.3 % in the whole population ($P = 0.76$); 74.6 % (presence) vs. 72.2 % (absence) in the conventional group ($P > 0.99$); and 94.7 % vs. 100 %, respectively, in the ES-LBD group ($P = 0.56$).

Stone clearance rates were not significantly different between patients in low-inclusion centers and high-inclusion centers, both in the whole population (57/70 [81.4 %] vs. 71/80 [88.8 %]; $P = 0.21$) or in the conventional group (21/31 [67.7 %] vs. 33/42, [78.6 %]; $P = 0.30$).

The conventional procedure failed in 19 patients, 15 of whom underwent a rescue ES-LBD procedure (after a median of 40 minutes [IQR 20 – 52] since the conventional procedure was attempted), which successfully cleared all stones.

Morbidity and mortality

Complications occurred in 9.3 % of patients in the conventional group and in 8.1 % of patients in the ES-LBD group ($P = 0.82$). To describe morbidity of each procedure, we selected all patients in whom the procedure chosen by randomization succeeded (54/73 patients in the conventional group and 74/77 patients in ESLBD group). Details are reported in ▶ **Table 2**. For all patients, intent-to-treat complications were also not significantly different between the conventional group (6.8 % [5/73]) and the ES-LBD group (7.80 % [6/77]; $P = 0.83$).

Rates of post-ERCP bleeding were not significantly different between groups ($P > 0.99$). Post-ERCP bleeding was reported in two patients in the conventional group, but no blood transfusion was required and bleeding could be managed conservatively (in one case with placement of a biliary covered stent). Post-ERCP bleeding was reported in three patients in the ES-LBD group: one patient did not require a blood transfusion, one patient received 2 units of blood, and the third patient required 8 units of blood, placement of a biliary stent, and a 22-day hospital stay.

There was only one case of acute pancreatitis, which occurred in the ES-LBD group and was severe. The condition finally resolved following medical care and a 19-day hospital stay. There were no cases of pancreatitis in the conventional group.

One case of perforation was recorded in the same ES-LBD patient who had presented severe bleeding and was treated with biliary stenting. This pneumoretroperitoneum was diagnosed on Day 1 by CT and resolved on Day 7.

Post-ERCP cholecystitis occurred in two patients (one in each group; $P > 0.99$).

There were no cases of CBD stone recurrence in either group at 30 days post-procedure.

Three patients died during the study: two in the conventional group and one in the ES-LBD group. None of the deaths were related to the ERCP procedure. One patient in the conventional group died from cerebral vascular disease 5 days post-ERCP, and another patient died as a result of myocardial infarction and cerebral vascular disease 21 days post-ERCP. The ES-LBD patient died from cardiac failure 24 hours post-ERCP.

Need for mechanical lithotripsy

Significantly more patients required subsequent mechanical lithotripsy in the conventional group (26/73 [35.62 %] vs. 3/77 [3.9 %]; $P < 0.001$).

We compared data from patients who were randomized to the conventional group and underwent mechanical lithotripsy (26/73) with all patients in whom ES-LBD was performed (77/77). Results are shown in ▶ **Table 3**.

▶ **Table 1** Comparison of demographic data, stone characteristics, and patient anatomic data between the two groups of patients.

	Conventional (n = 73)	ES-LBD (n = 77)	Total (n = 150)	*P* value
Age, mean (SD), years	80.9 (11.6)	76.7 (11.9)	78.8 (11.9)	0.03
Sex, male/female, n	31/42	26/51	57/93	0.27
Indications for ERCP, n (%)				0.55
▪ Acute cholangitis	46 (63.0)	44 (57.1)	90 (60.0)	0.46
▪ Acute jaundice	6 (8.2)	13 (16.9)	19 (12.7)	0.11
▪ Pain	12 (16.4)	13 (16.9)	25 (16.7)	0.94
▪ Abnormal liver function tests	5 (6.9)	3 (3.9)	8 (5.3)	0.49[1]
▪ Radiological abnormalities[2]	4 (5.5)	4 (5.2)	8 (5.3)	> 0.99[1]
Stone characteristics				
▪ Number of stones, mean (SD)	3.6 (3.8)	2.8 (3.3)	3.2 (3.5)	0.19
▪ Size of stones, mean (SD), mm				
– Largest diameter of the biggest stone	16.2 (3.5)	16.5 (3.3)	16.3 (3.4)	0.64
– Smallest diameter of the biggest stone	14.9 (1.9)	15.2 (1.8)	15.1 (1.9)	0.39
Patient anatomic data				
▪ CBD diameter (mm), mean (SD)	16.9 (3.9)	16.8 (4.7)	16.9 (4.3)	0.84
▪ Papillary diverticula, (%)	24.7	26.0	25.3	0.85
▪ Cholecystectomy (%)	31.9	39.5	35.9	0.34
Prior endoscopic sphincterotomy (%)	0	1.30	0.67	> 0.99

ES-LBD, endoscopic sphincterotomy plus large-balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct.
[1] Fisher's exact test.
[2] Radiological abnormalities included findings of CBD stones or dilated CBD on ultrasonography, computed tomography or magnetic resonance cholangiopancreatography.

Cost and duration of procedures

The procedure times and costs were measured for the 128 successful procedures plus the 7 failed procedures with no switch. The median procedure time was 35 minutes (IQR 22 – 48) in the conventional group and 30 minutes (IQR 25 – 50) in the ES-LBD group ($P = 0.98$). The median cost of consumables was €449 (SD 210; equivalent to $210) in the conventional group and €447 (SD 102; $543) in the ES-LBD group ($P = 0.30$).

These data showed no significant difference between the two groups. However, the cost and procedure time became significantly higher for patients in the conventional group who needed mechanical lithotripsy vs. patients in the ES-LBD group (€624 [$709] vs. €477 [$543], respectively, $P = 0.03$; and 45 minutes [IQR 35 – 65] vs. 30 minutes [IQR 25 – 50], respectively, $P = 0.02$) (▶ **Table 3**).

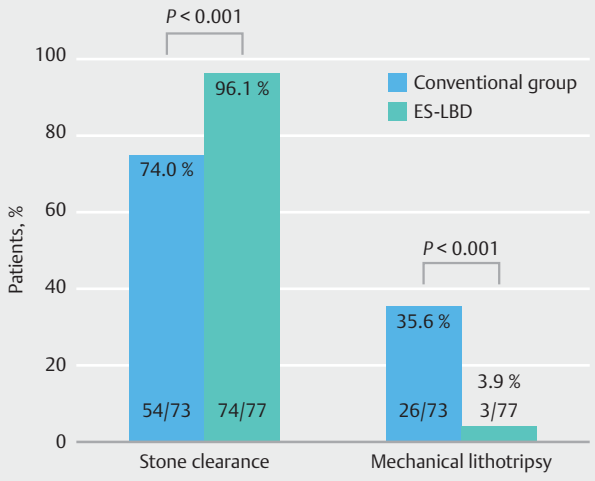
Discussion

This study demonstrated that ES-LBD is significantly superior to endoscopic sphincterotomy for retrieval of CBD stones ≥ 13 mm in diameter. In addition, ES-LBD resulted in a reduced need for mechanical lithotripsy to retrieve the stones. Morbidity rates were low and comparable in both groups, even when a complete endoscopic sphincterotomy was performed prior to large-balloon dilation in the ES-LBD group. Furthermore, the cost of endotherapy devices used for ERCP was significantly lower for patients in the ES-LBD group compared with patients in the conventional group who needed mechanical lithotripsy.

This is the first randomized multicenter study to evaluate ES-LBD with complete endoscopic sphincterotomy in patients with exclusively large CBD stones. The study demonstrated the feasibility, morbidity, and efficacy of large-balloon dilation when performed for stones that could not be retrieved despite a complete endoscopic sphincterotomy.

Ersoz et al. first described the use of ES-LBD for patients with CDB stones that were too big to be retrieved by basket or balloon extraction after complete endoscopic sphincterotomy [4]. In this original description of the procedure, ES-LBD had a high overall success rate of 93 %, and an acceptable morbidity rate of 15 %.

Since then, six randomized studies have confirmed the safety of ES-LBD, but its real benefit has remained controversial [11 – 16]. Two of the studies concerned patients with large bile duct stones [12, 13], and in two others, large-balloon dilation was performed after a large endoscopic sphincterotomy [15,



▶ **Fig. 2** Comparison of stone clearance rate and mechanical lithotripsy rate between the two groups. ES-LBD, endoscopic sphincterotomy plus large-balloon dilation.

16, but none of these studies addressed these combined features, which more closely reflects the real-life clinical situation (large-balloon dilation for large stones after a large endoscopic sphincterotomy). To clarify the ES-LBD benefit, four recently published meta-analyses were carried out [18 – 21], all of which concluded the equivalence of endoscopic sphincterotomy and ES-LBD for stone clearance rate in one session, even if significantly less mechanical lithotripsy was performed in ES-LBD patients.

These results can be explained by the fact that most randomized studies, especially for the largest series [11, 14, 15], have evaluated endoscopic sphincterotomy vs. ES-LBD without considering stone size. However, it is precisely stone diameter that is the main cause of incomplete stone extraction in the first session.

Only two studies have randomized patients with large stones [12, 13]. The first demonstrated that ES-LBD and endoscopic sphincterotomy were equally effective for stone extraction, but the study was limited by its small size (n = 55) [12]. Surprisingly, even though median stone diameter was 21 mm, mechanical lithotripsy was used in less than one third of cases in the study. The second randomized study included 132 patients with large stones (bigger stone diameter ≥ 15 mm), and showed a higher efficacy of ES-BLD, with a threefold reduction in the need for mechanical lithotripsy in the ES-LBD group [13]. One issue common to both of these studies is that large-balloon dilation was performed after a limited endoscopic sphincterotomy, whereas in routine practice the decision to perform large-balloon dilation or mechanical lithotripsy intervenes only after standard (i. e. complete) endoscopic sphincterotomy has already been attempted. This discrepancy can be explained by the fact that in most randomized studies, a "small" endoscopic sphincterotomy was proposed in an effort to minimize the complication rates, especially the bleeding risk [11 – 14, 22]. However, such a cautious attitude is no longer supported by current evidence, as several retrospective or uncontrolled studies as well as randomized studies comparing ES-LBD vs. endoscopic sphincterotomy, with or without mechanical lithotripsy (including the current study), have not found higher morbidity rates with large-balloon dilation after complete endoscopic sphincterotomy [15, 16, 23]. These data suggest that a limited endoscopic sphincterotomy is not beneficial, a notion that is supported by a recent randomized study comparing ES-LBD with mechanical lithotripsy after complete endoscopic sphinc-

▶ **Table 2** Comparison of morbidity and mortality of successful procedures.

	Conventional (n = 54)	ES-LBD (n = 74)	Total (n = 128)	*P* value
Morbidities, n (%)	5 (9.3)	6 (8.1)	11 (8.6)	0.82
Bleeding, n (%)	2 (3.7)	3 (4.1)	5 (3.9)	> 0.99†
▪ Mild	2	2	4	> 0.99†
▪ Severe	–	1	1	> 0.99†
Perforation, n (%)	–	1 (1.4)	1 (0.8)	> 0.99†
Pancreatitis, n (%)	–	1 (1.4)	1 (0.8)	> 0.99†
▪ Mild	–	–	–	–
▪ Severe	–	1	1	> 0.99[1]
Cholangitis, n (%)	–	–	–	–
Cholecystitis, n (%)	1 (1.9)	1 (1.4)	2 (1.6)	> 0.99[1]
Mortality, n (%)	2[2] (3.7)	1[2] (1.4)	3[2] (2.3)	0.57[1]

ES-LBD, endoscopic sphincterotomy plus large-balloon dilation.
[1] Fisher's exact test.
[2] Deaths not related to endoscopic retrograde cholangiopancreatography.

▶ **Table 3** Comparison of conventional treatment plus mechanical lithotripsy and endoscopic sphincterotomy with large-balloon dilation.

	Conventional + mechanical lithotripsy (n = 26)	ES-LBD (n = 77)	*P* value
Stone characteristics			
▪ Number of stones, mean (SD)	3.8 (4.0)	2.8 (3.3)	0.06
▪ Size of stones, mean (SD), mm			
– Largest diameter of the biggest stone	17.4 (4.0)	16.5 (3.3)	0.21
– Smallest diameter of the biggest stone	15.7 (2.2)	15.2 (1.8)	0.33
CBD diameter, mean (SD), mm	17.1 (4.4)	16.8 (4.7)	0.66
Stone clearance rate, n (%)	16 (61.5)	74 (96.1)	< 0.001[1]
Cost of consumables, mean (SD), €	624 (249)	477 (102)	0.03
Procedure time, median (IQR), minutes	45 (35 – 65)	30 (25 – 50)	0.02
Recurrence of BDS within 30 days	–	–	–

ESLBD, endoscopic sphincterotomy plus large-balloon dilation; CBD, common bile duct; BDS, bile duct stone.
[1] Fisher's exact test.

terotomy for large CBD stones (> 12 mm); the study was stopped before reaching the mid-enrollment stage owing to significantly higher morbidity associated with mechanical lithotripsy [24].

Therefore, a first important and practical conclusion of our study is that ES-LBD should now be proposed as the first-step treatment for patients in whom CBD stone extraction fails following complete endoscopic sphincterotomy in most routine practice situations.

However, the difficulty in clearing CBD stones stems not just from the size of large stones but also stricture of the distal CBD [25]. Even if ES-LBD is feasible (but not necessarily safe) in cases of distal CBD stricture, we decided to exclude patients presenting this anatomical condition [25, 26]. Consequently, we cannot advocate ES-LBD for the treatment of CBD stones in cases of stricture of the distal CBD.

Two further key considerations are overall procedure time and fluoroscopy time. These factors have only been evaluated in one randomized study on 462 patients, where Li et al. reported lower overall procedure time and fluoroscopy time for ES-LBD than endoscopic sphincterotomy (38 ± 15 vs. 47 ± 20 minutes, $P < 0.05$; and 17 ± 7 vs. 26.5 ± 11, $P < 0.05$, respectively) [11]. Our results were consistent with this study, with a significantly lower procedure time in the ES-LBD group compared with patients in the conventional group undergoing mechanical lithotripsy (▶ **Table 3**).

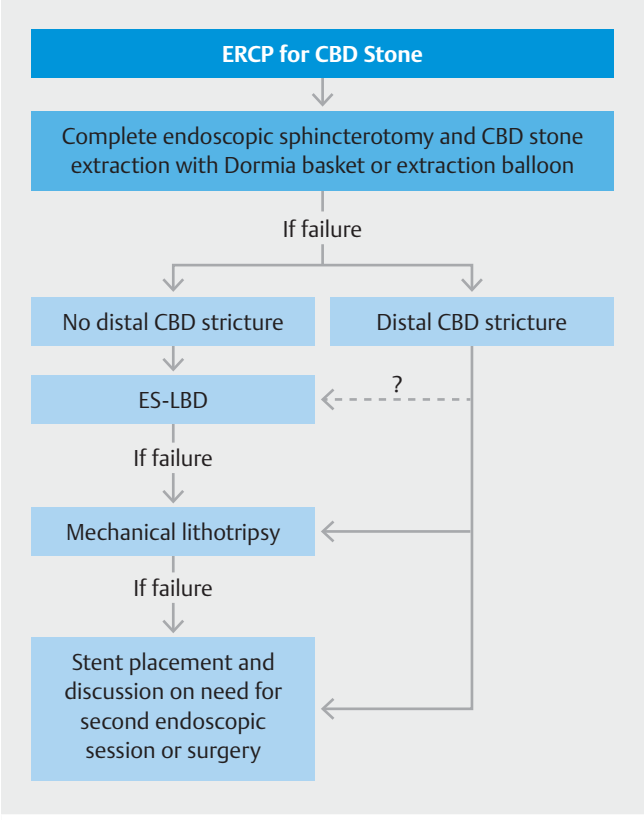
Interestingly, we also report a significantly lower cost of procedure-related endotherapy devices in the ES-LBD group vs. endoscopic sphincterotomy with mechanical lithotripsy group (▶ **Table 3**) but not vs. the conventional group as a whole. Indeed, in the ES-LBD group, large-balloon dilation was performed after endoscopic sphincterotomy in 100 % of cases, whereas mechanical lithotripsy was needed in only 36 % of cases after endoscopic sphincterotomy in the conventional group. Therefore, procedures necessitating only endoscopic sphincterotomy were shorter and less expensive. A lower cost of hospital stay for ES-LBD vs. endoscopic sphincterotomy was also found in the only other published randomized study that evaluated cost [16].

In the current study, rates of procedure-related short-term complications were not significantly different between the two groups, and were similar to data from previous randomized studies [11 – 16]. Consistently with other studies, periampullary diverticulum was present in 25 % of cases in our study but did not appear to affect the CBD stone clearance or morbidity rates. This issue was recently studied in a large, retrospective, single-center series on 223 patients, showing similar results [27].

The suspected increased risk of bleeding after ES-LBD in a large retrospective study [22], especially in the case of complete endoscopic sphincterotomy, was not found in the current study. Indeed, bleeding was not significantly different between the ES-LBD and conventional groups, as in all other randomized studies [11 – 16] except one, which reported significantly lower bleeding after ES-LBD (2 % in ES-LBD vs. 5 % in the endoscopic sphincterotomy group, $P = 0.04$), probably as a result of balloon compression on the sphincterotomy site [11].

The risk of acute pancreatitis following ESLBD was not higher than after endoscopic sphincterotomy, as observed in most other studies and all randomized studies [7, 11 – 16].

The most serious adverse event after ES-LBD is perforation, which occurs in less than 0.5 % of cases [6]. In our study, the perforation rate was very low and similar to previous randomized studies [11 – 16]. However, a retrospective multicenter study in 946 patients found stricture of the distal CBD to be a strong and independent risk factor for perforation in multivariate analysis (odds ratio 17) [22]. Conversely, two randomized studies that included 18.2 % and 38 % of patients with distal CBD tapering, found no difference in perforation rates between the groups [12, 13]. In the current study, we decided not to in-



▶ **Fig. 3** Algorithm of endoscopic management of large common bile duct stones. ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; ES-LBD, endoscopic sphincterotomy plus large-balloon dilation.

clude patients with distal CBD stricture. Safety and efficacy of ES-LBD in patients with distal CDB stricture should be evaluated in further randomized studies.

Our study has limitations. First, low rates of patient inclusion in the study were noted in several centers, as is common in multicenter studies owing to variable contribution of respective investigators. It is possible that not all eligible patients were invited for inclusion in the study at these centers. The large number of centers is an advantage for the reproducibility of the results, but is also a weakness if the study includes too many low-inclusion centers. Second, patient follow-up was limited to 1 month, which means that no longer-term follow-up data are available for evaluation. Although no recurrence of CBD stones was noted during this period of time, further biliary events such as CBD recurrence or stenosis cannot be ruled out. Third, patient inclusion (and randomization) was based on CBD stone size on cholangiogram, prior to any attempt to extract the stones after endoscopic sphincterotomy. This design does not therefore reproduce "real-life" conditions, but we believe that this approach was much more robust to avoid other potential inclusion biases. This decision was prompted by the fact that the stone size inclusion criterion was reliable, accurate, and reproducible in the setting of a large multicenter study, in contrast to the variety of methods and efforts available for obtaining successful stone extraction. An added advantage of this design was that it allowed us to compare the need for mechanical lithotripsy between the groups. On the other hand, the primary end point of this study was not to compare ES-LBD with mechanical lithotripsy in the event of failed large stone extraction after endoscopic sphincterotomy. Only one randomized study has compared ES-LBD with mechanical lithotripsy in this situation, but that study was unfortunately stopped before reaching mid-enrollment, owing to morbidity associated with mechanical lithotripsy [24].

From the results of this large, randomized, multicenter study, we conclude that ES-LBD is a simple, reproducible, and effective technique for the removal of CBD stones ≥ 13 mm in the absence of distal CBD stricture. The cost of endotherapy devices and procedure times appear to be lower compared with endoscopic sphincterotomy with mechanical lithotripsy. The study design does not lead to the conclusion that complete endoscopic sphincterotomy is superior to limited endoscopic sphincterotomy before large-balloon dilation (also safe and effective), but knowledge of the safety and efficacy of large-balloon dilation after complete endoscopic sphincterotomy, allows large-balloon dilation in routine practice when the stone cannot be extracted after a complete endoscopic sphincterotomy has been performed. Based on our results, we propose an algorithm of endoscopic treatment for CBD stones (▶ **Fig. 3**). If CBD stone(s) cannot be extracted after a complete endoscopic sphincterotomy, ES-LBD should be considered as the first-line treatment step, before performing mechanical lithotripsy. Our crossover procedure data found that ES-LBD can also be useful as a rescue option after failed mechanical lithotripsy. In the event of a final failure, a stent should be inserted awaiting a second endoscopic session or surgery. Given that there is still a lack of data on ES-LBD in cases involving distal CBD stricture, further prospective studies should evaluate the risks of complications with ES-BLD and determine the optimal therapeutic algorithm in this specific situation.

Competing interests

None

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