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A Preliminary Comparison of Endoscopic Sphincterotomy, Endoscopic Papillary Large Balloon Dilation, and Combination of the Two in Endoscopic Choledocholithiasis Treatment

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Background: Endoscopic retrograde cholangiopancreatography (ERCP) is commonly performed to remove bile duct stones. Endoscopic sphincterotomy (EST), endoscopic papillary large balloon dilation (EPLBD), and endoscopic sphincterotomy plus large balloon dilation (ESLBD) are 3 methods used to enlarge the papillary orifice, but their efficacy and safety remains controversial. This study aimed to compare these methods for treating common bile duct (CBD) stones.

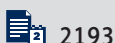
Material/Methods: Between July 2011 and December 2013, 255 consecutive patients with proven CBD stones were randomly assigned to EST, EPLBD, or ESLBD (n=85/group). The stone clearance rate, cannulation time, procedural time, frequency of mechanical lithotripsy (ML) use, complications, mortality, and procedural costs were compared.

Results: A total of 92.9%, 91.8%, and 96.5% of the patients in the EST, EPBD, and ESBD groups had stones cleared at first ERCP ($P=0.519$), respectively. ML was used in 9.4%, 14.1%, and 8.2% of the patients in the EST, EPLBD, and ESLBD groups ($P=0.419$). The costs of EPLBD were higher than EST and lower than ESLBD ($P<0.001$). Complications occurred in 4.7%, 4.7%, and 5.9% of the patients in the EST, EPLBD, and ESLBD groups, respectively ($P=1.000$). The proportion in severity was similar ($P=0.693$). None of the patients died after the procedures. The rates of the post-ERCP pancreatitis, cholangitis, and bleeding were similar among all groups.

Conclusions: EST, EPLBD, and ESLBD might clear CBD stones with equal efficacy and safety. A non-inferiority trial might be necessary to confirm these results.

MeSH Keywords: **Cholangiopancreatography, Endoscopic Retrograde • Common Bile Duct • Gallstones Lithotripsy • Sphincterotomy, Endoscopic**

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Background

Endoscopic sphincterotomy (EST) is the standard method for enlarging the bile duct opening in the duodenum before stone removal during endoscopic retrograde cholangiopancreatography (ERCP). Although EST is effective, it permanently destroys the biliary sphincter [1]. Therefore, subsequent duodenobiliary reflux can occur with bacterial contamination and chronic inflammation of the biliary system, which can lead to long-term problems [1].

Recently, endoscopic sphincterotomy plus large balloon dilation (ESLBD) has been reported for treating large common bile duct (CBD) stones [2]. Endoscopic papillary balloon dilation (EPBD) is another alternative technique to enlarge the papillary orifice for stone retrieval, with the potential advantage of biliary sphincter function preservation. However, EPBD might carry an increased risk of pancreatitis due to edema and/or spasm from dilation trauma [3–5].

Some previous reports indicated that ESLBD reduced the need for mechanical lithotripsy (ML) in large CBD stone extraction [6,7], while others did not report any difference [8,9]. Furthermore, a number of studies, along with a meta-analysis on EST vs. EPBD, suggested that they were not significantly different in terms of stone clearance rates [4,5], while other studies indicated a significantly higher stone clearance rate in the EST group [3]. Other published studies and a meta-analysis of 3 randomized controlled trials (RCTs) on EST vs. ESLBD showed that there was no significant difference between EST and ESLBD in terms of stone clearance rates.

The present preliminary study is the first to compare the advantages and disadvantages of these 3 methods (EST, endoscopic papillary large balloon dilatation (EPLBD), and ESLBD), being the first to do so. Therefore, we carried out this preliminary randomized trial to evaluate the benefits and risks of EST, EPLBD, and ESLBD for the extraction of CBD stones. Furthermore, the surgical efficacy, postprocedural safety, and economic factors were compared. The results of this study could provide the basis for large-scale multicenter clinical trials.

Material and Methods

This was a prospective randomized study conducted in Nanfang Hospital between July 2011 and December 2013. The study protocol was approved by the Medical Ethics Committee of the Nanfang Hospital. All patients signed an informed consent before ERCP. The study was registered with chictr.org (ChiCTR-TRC-12002341).

Patients

The inclusion criteria were: 1) patients aged ≥ 18 years and 2) CBD stones confirmed by cholangiogram (≥ 10 mm in maximum diameter). The exclusion criteria were: 1) septic shock; 2) acute pancreatitis; 3) coagulopathy (international normalized ratio of >1.5 , partial thromboplastin time greater than twice that of control); 4) platelet count of $<50,000 \times 10^3/\mu\text{L}$; 5) prior sphincterotomy or dilation; 6) biliary strictures; 7) Billroth-II or Roux-en-Y anatomy; 8) concomitant pancreatic or biliary malignancies; 9) pregnancy; 10) requirement of precut sphincterotomy for bile duct access; or 11) inability to give informed consent.

Interventions

The moderate sedation used for the procedure consisted of a combination of meperidine and diazepam along with anisodamine, as needed for duodenal relaxation. Lopromide was used as the contrast agent. ERCP was performed in the prostrate position. The patients underwent continuous cardiopulmonary monitoring throughout the procedure. ERCPs were performed by experienced endoscopists ($n=5$) using side-viewing endoscopes (JF-260 or TJF-260; Olympus Optical Co. Ltd., Tokyo, Japan). Selective cannulation of the bile duct was attempted using a 20-mm cut wire sphincterotome (Boston Scientific, Natick, MA) with a 0.035" guide wire (Boston Scientific, Natick, MA).

Patients were randomized using a computer-generated random number table (prepared by a statistician) into the EST, EPLBD, or ESLBD groups after bile duct access was achieved and a cholangiogram confirmed the presence of the CBD stones. The sizes of the stones were estimated based on the size of the duodenoscope mirror body diameter (12 mm).

For the EST group, sphincterotomy was performed with a 20 mm cut-wire sphincterotome (Boston Scientific, Natick, MA). The length of the incision was decided by the endoscopist according to the size of the stones. The ERBE generator (ICC 200; ERBE, Tübingen, Germany) with a blended current was also used.

For the EPLBD group, dilation of the sphincter was performed with a 5.5-cm wire-guided balloon dilation catheter (Boston Scientific, Natick, MA or Cook Medical, Limerick, Ireland). The balloon was passed over a prepositioned guide wire and was centered at the sphincter. Under endoscopic and fluoroscopic control, the balloon was gradually inflated with diluted contrast agent until the complete disappearance of the balloon waist. The size of the balloon was gauged by the size of the CBD. The minimum and maximum diameters of the balloon were 10 and 15 mm, respectively.

Table 1. Characteristics of the patient.

	EST (n=85)	EPLBD (n=85)	ESLBD (n=85)	P
Sex (F/M)	42/43	40/45	39/46	0.896
Age (y) ^a	59±16	62±17	63±16	0.154
Periampullary diverticulum	27	26	46	0.002
CBD size (mm) ^b	12 (11–40)	12 (11–30)	12 (11–30)	0.071
Stone size (mm) ^b	10 (10–40)	10 (10–30)	10 (10–30)	0.877
Stone number				0.910
1	48 (56.47%)	47 (55.29%)	44 (51.76%)	
2	11 (12.94%)	10 (11.76%)	12 (14.12%)	
3	3 (3.53%)	7 (8.24%)	5 (5.88%)	
>3	23 (27.06%)	21 (24.71%)	24 (28.24%)	

^a Values expressed as mean ±SD; ^b values expressed as medians (range). EST – endoscopic sphincterotomy; EPLBD – endoscopic papillary large balloon dilation; ESLBD – endoscopic sphincterotomy plus large balloon dilation; CBD – common bile duct.

For the ESLBD group, a limited sphincterotomy measuring up to one- to two-thirds of the papilla was first performed, followed by dilation. After the procedure, stones were removed by standard methods, including retrieval baskets (Olympus Co. Ltd., Tokyo, Japan) and extraction balloon (Cook Medical, Limerick, Ireland). ML (Olympus Co. Ltd., Tokyo, Japan) was used to crush the stones, when necessary. An occlusion cholangiogram was obtained at the end of the ERCP, followed by a nasobiliary drain (Boston Scientific, Natick, MA or Cook Medical, Limerick, Ireland) insertion for drainage, which was performed in all patients to avoid bias. After ERCP, patients were kept in the ward to be monitored for any complications. Patients were discharged when the acute condition was resolved.

Measurements

All patients were interviewed by phone 30 days after ERCP in order to assess the potential complications. The primary outcome was the stone clearance rate at the initial ERCP. Secondary outcomes included cannulation time, procedural time, frequency of ML use, 30-day complications and mortality, and procedural cost. Complete stone clearance was defined as the absence of filling defects on occlusion cholangiogram. The cannulation time was calculated from the time of sphincterotome touching the papilla to a successful selective cannulation of the bile duct. The procedural time was the time from a successful selective cannulation of the bile duct up to the nasobiliary drain insertion. Complication assessment was based on the intent-to-treat principle and were defined and graded according to the Cotton et al.'s system [10]. Post-ERCP pancreatitis was defined as signs and symptoms of acute pancreatitis following ERCP, with elevated levels of pancreatic enzymes [11].

Statistical analysis

Data were analyzed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Data normality was assessed using the Kolmogorov-Smirnov test. Data are expressed as means ± standard deviation (SD) or frequencies. The differences between groups were compared using analysis of variance (one-way ANOVA) for parametric data, Kruskal-Wallis test for nonparametric data, and Fisher's exact or Pearson chi-square tests for proportions and frequencies. Differences were considered statistically significant if the 2-sided P-value was <0.05.

Results

Characteristics of the patients

From July 2011 to December 2013, 255 consecutive patients were enrolled in the study. Table 1 shows the patient demographics with no difference in baseline characteristics among the 3 groups, except that more patients who underwent ESLBD had periampullary diverticulum.

Characteristics of the procedures

The procedural details of the 3 groups of patients are shown in Table 2. There were no differences in cannulation time, guide wire injection time into the pancreatic duct, and time to complete the procedure. Similar rates of stone clearance were observed among the 3 groups. A total of 92.9%, 91.8%, and 96.5% of the patients in the EST, EPLBD, and ESLBD groups, respectively, had their stones cleared during the initial ERCP

Table 2. Characteristics of the procedures.

	EST (n=85)	EPLBD (n=85)	ESLBD (n=85)	P
Cannulation time (min) ^a	2 (1–14)	2 (1–8)	2 (1–11)	0.323
Guide wire injection ^{a,c}	0 (0–3)	0 (0–3)	0 (0–3)	0.273
Procedural time (min) ^b	20±11	22±10	20±10	0.312
Stone clearance rates, n (%)	79 (92.9)	78 (91.8)	82 (96.5)	0.519
Stone diameter				
<15 mm, n total; n (%) cleared ^d	70; 69 (98.6)	69; 65 (94.2)	68; 67 (98.5)	0.330
≥15 mm, n total; n (%) cleared ^d	15; 10 (66.7)	16; 13 (81.3)	17; 15 (88.2)	0.327
Stone number				
≤3, n total; n (%) cleared ^d	62; 62 (100)	64; 61 (95.3)	61; 60 (98.4)	0.274
>3, n total; n (%) cleared ^d	23; 17 (73.9)	21; 17 (81.0)	24; 22 (91.7)	0.270
Mechanical lithotripsy, n (%)	8 (9.4)	12 (14.1)	7 (8.2)	0.419
Procedural costs ^a	13,199 (13199–17719)	17,021 (17021–21541)	18,021 (18021–22541)	<0.001
Mechanical lithotripsy, n (%)	8 (9.4)	12 (14.1)	7 (8.2)	0.419
Stone diameter				
<15 mm, n total; n (%) cleared ^d	70; 4 (5.7)	69; 4 (5.8)	68; 4 (5.9)	1.000
≥15 mm, n total; n (%) cleared ^d	15; 4 (26.7)	16; 8 (50.0)	17; 3 (17.6)	0.151
Stone number				
≤3, n total; n (%) cleared ^d	62; 4 (6.5)	64; 8 (12.5)	61; 4 (6.6)	0.417
>3, n total; n (%) cleared ^d	23; 4 (17.4)	21; 4 (19.0)	24; 3 (12.5)	0.854

^a Values expressed as medians (range); ^b values expressed as mean ±SD; ^c guide wire injection means times when the guide wire was injected into pancreatic duct; ^d the first n indicate the number of patients in the category. The second n indicate the number of patients with cleared stones. The % indicate the percentage of patients with cleared stones. EST – endoscopic sphincterotomy; EPLBD – endoscopic papillary large balloon dilation; ESLBD – endoscopic sphincterotomy plus large balloon dilation.

(*P*=0.519). ML was used in 9.4% (8/85), 14.1% (12/85), and 8.2% (7/85) of the patients in the EST, EPLBD, and ESLBD groups (*P*=0.419), respectively. The procedural costs were also compared between the groups; the costs of EPLBD were higher than EST and lower than ESLBD (*P*<0.001).

Subgroup analysis was therefore undertaken with the patients classified according to the stone size and stone number. The stone clearance rates and frequency of ML use were also similar among the groups.

Mortality and complications

None of the patients died. Table 3 shows the complications within 30 days after ERCP; they occurred in 4.7%, 4.7%, and

5.9% of the patients in the EST, EPLBD, and ESLBD groups (*P*=1.000), respectively. The proportion in severity was similar (*P*=0.693) with no significant difference in the rates of post-ERCP pancreatitis, cholangitis, and bleeding among the groups.

Discussion

The aim of the present study was to evaluate the benefits and risks of EST, EPLBD, and ESLBD for the extraction of CBD stones. This is the first study directly comparing the 3 approaches. The stone clearance rate was similar among the 3 groups, as well as the use of ML and the rate and severity of complications. The costs of EPLBD were higher than EST and lower than ESLBD (*P*<0.001). There was no mortality after the procedures. The

Table 3. Mortality and complications within 30 days after ERCP.

	EST (n=85)	EPLBD (n=85)	ESLBD (n=85)	P
Mortality, n (%)	0 (0)	0 (0)	0 (0)	1.000
Morbidities, n (%)	4 (4.7)	4 (4.7)	5 (5.9)	1.000
Mild, n (%)	2 (2.4)	3 (3.5)	4 (4.7)	0.693 ^a
Moderate, n (%)	0 (0)	1 (1.2)	1 (1.2)	
Severe, n (%)	2 (2.4)	0 (0)	0 (0)	
Pancreatitis, n (%)	2 (2.4)	2 (2.4)	2 (2.4)	1.000
Cholangitis, n (%)	1 (1.2)	1 (1.2)	2 (2.4)	1.000
Bleeding, n (%)	1 (1.2)	1 (1.2)	1 (1.2)	1.000

^a Value for the proportions of severity. EST – endoscopic sphincterotomy; EPLBD – endoscopic papillary large balloon dilation; ESLBD – endoscopic sphincterotomy plus large balloon dilation.

rates of the post-ERCP pancreatitis, cholangitis, and bleeding were similar among all groups. These results provide the basis for a multicenter randomized non-inferiority trial.

Previous studies compared 2 approaches at a time but yielded conflicting results. A number of studies along with a meta-analysis on EST vs. EPBD have suggested that they were not significantly different in terms of stone clearance rates [4,5,12–17], while other studies indicated a significant higher stone clearance rate in the EST group [3,18]. Published studies and a meta-analysis of 3 RCTs on EST vs. ESLBD showed that there was no significant difference between EST and ESLBD in terms of stone clearance rates [6–9,19]. The results of the present study further suggested similar stone clearance rates for EST, EPLBD, and ESLBD.

As for subgroup analysis, Vlavianos et al. [15] have indicated that there was no significant difference between EST and EPBD in stones larger than ≥ 10 –15 mm. Furthermore, Heo et al. [9] confirmed the lack of significant difference between EST and ESLBD in stones larger than 15 mm. In the present study, EST, EPLBD and ESLBD had similar stone clearance rates in stones ≥ 15 mm.

Several studies and a meta-analysis on EST vs. EPBD have suggested that EPBD resulted in a significantly higher frequency of ML use [3,12,13,17], while other reports indicated no significant difference [5,14,18]. Some other studies and a meta-analysis of 3 RCTs on EST vs. ESLBD have shown no significant difference between EST and ESLBD in terms of ML use [7–9,19]. However, the latest RCT suggested a significantly higher frequency of ML use in the EST group compared with that of the ESLBD group. The results of the present study further showed that EST, EPLBD, and ESLBD had similar ML use. This might have been caused by the low number of stones

≥ 15 mm in the present study (17.6% of EST, 18.8% of EPLBD, and 20.0% of ESLBD).

In a subgroup analysis, Watanabe et al. [3] observed a significantly higher frequency of ML use in the EPBD group compared with that of the EST group in stones ≥ 10 mm. Teoh et al. [6] and Kim et al. [7] showed a significantly higher frequency of ML use in the EST group compared with the ESLBD group in stones > 15 mm, while Heo et al. [9] suggested no significant difference between EST and ESLBD in terms of ML use. In the present study, EST, EPLBD and ESLBD had a similar frequency of ML use in stones ≥ 15 mm.

A number of reports on EST vs. EPBD have indicated no significant differences in the overall complication rate and post-ERCP pancreatitis in EST and EPBD [12–14]. However, the study by Fujita et al. [5] and a meta-analysis [17] have shown that EST and EPBD did not have a significant difference in their overall complication rates, but a significantly higher risk of post-ERCP pancreatitis was reported for EPBD. In addition, a multicenter study in the United States have suggested that EPBD had a significantly higher risk of both overall complication rate and post-ERCP pancreatitis along with 2 deaths due to pancreatitis following dilation and none with sphincterotomy. Previous studies and a meta-analysis of 3 randomized controlled trials (RCTs) on EST vs. ESLBD reported the complication rates and post-ERCP pancreatitis [6,7,9,19]. Likewise, in the present study, EST, EPLBD, and ESLBD had similar complication rate and post-ERCP pancreatitis. This might have been due to the adequately enlarged papillary orifices and nasobiliary drains in all patients.

There were a few drawbacks to the current study. On one hand, the proportion of stones ≥ 15 mm was low, which could have potentially resulted in a small sample size for the stones

≥15 mm. Increasing the sample size for the stones ≥15 mm might detect some differences among EST, EPLBD, and ESLBD in terms of ML use. On the other hand, our study only assessed short-term complications, not long-term complications, which could be important to evaluate the safety of the techniques. This could be easily addressed by patient telephone follow-ups for the assessment of the complications. The present was powered as a superiority trial, and failed to observe differences between groups, but was underpowered to reach non-inferiority conclusions. Therefore, the results of the present study should be used as a basis to plan a multicenter non-inferiority randomized trial of these 3 approaches.

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Conclusions

In conclusion, EST, EPLBD, and ESLBD might clear CBD stones with equal efficacy and safety. There was no difference among the groups except for the cost factor. A larger sample size or a non-inferiority trial might be necessary to confirm these results.

Conflicts of interest

The authors declare that they have no conflicts of interest.