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Which Is the Better Treatment for the Removal of Large Biliary Stones? Endoscopic Papillary Large Balloon Dilation versus Endoscopic Sphincterotomy

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See editorial on page 339.

Background/Aims: We evaluated the efficacy and cost-effectiveness of endoscopic papillary large balloon dilation (EPLBD) for large common bile duct (CBD) stone removal compared with endoscopic sphincterotomy (EST). **Methods:** A total of 1,580 patients who underwent endoscopic CBD stone extraction between January 2001 and July 2010 were reviewed. The following inclusion criteria were applied: choledocholithiasis treated by EPLBD with minor EST or EST with mechanical lithotripsy; and follow-up >9 months after treatment. **Results:** Forty-nine patients with EPLBD and 41 with EST were compared. There was no significant difference in the complication rates and stone recurrence rates between the two groups. However, significantly more endoscopic retrograde cholangiopancreatography (ERCP) sessions were required in the EST group to achieve the complete removal of stones (1.7 times vs 1.3 times; p=0.03). The mean cost required for complete stone removal per patient was significantly higher in the EST group compared to the EPLBD group (USD $1,644 vs $1,225, respectively; p=0.04). Dilated CBD was the only significant factor associated with recurrent biliary stones (relative risk, 1.09; 95% confidence interval, 1.02 to 1.17; p=0.02). **Conclusions:** EPLBD is the better treatment (compared to EST) for removing large CBD stones because EPLBD requires fewer ERCP sessions and is less expensive. **(Gut Liver 2014;8:438-444)**

Key Words: Choledocholithiasis; Endoscopic papillary large balloon dilation; Sphincterotomy, endoscopic; Mechanical lithotripsy

INTRODUCTION

Endoscopic sphincterotomy (EST) is the commonly used endoscopic technique to remove common bile duct (CBD) stones.[1] However, EST carries an 8% to 12% risk of acute complications such as pancreatitis, cholangitis, bleeding, and perforation.[2,3] Therefore, endoscopic papillary balloon dilation (EPBD) using balloon diameters of 6 to 10 mm was developed as an alternative method to EST to lower the acute complications risk by causing less trauma to the biliary sphincter.[4] EPBD is a safe and effective technique for removal of small to moderate sized stones, but it is inappropriate for removal of larger stones since EPBD does not enlarge the bile duct opening to the same extent as EST.[3] Thus, endoscopic papillary large balloon dilation (EPLBD) using balloon diameters of 12 to 20 mm combined with EST was introduced for removal of large CBD stones.[5] However, EPLBD was not fully accepted for the risk of potentially serious adverse events, such as pancreatitis and bile duct perforation.[6-8] There are still many controversies in safety issues using EPLBD, and recently multicenter studies and meta-analysis reported that EPLBD is a safe and effective therapeutic approach for retrieval of large stones.[7,9,10]

Considering long-term outcome, EPBD can be better treatment of choice for extracting CBD stones since it still preserves the function of sphincter muscle than EST in theory. Preserving sphincter muscle would be more beneficial to prevent recurrent biliary stones since subsequent duodenobiliary reflux and bacterial contamination are known to increase the tendency of recurrence.[11-14] However, there is no report about the physiologic and anatomical changes of the sphincter after EPLBD. Recent retrospective studies reported that the recurrence rate of choledocholithiasis was similar between EPLBD with limited

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EST and EST alone groups.[15,16] However, these studies have some pitfalls which underestimated the preventive efficacy of recurrent stones by EPLBD since they did not take it account the fact that the patients who underwent EPLBD were more likely to have larger stones which could affect the biliary stone recurrence rate.[17,18] Stefanidis *et al*.[19] reported that EST with EPLBD was equally effective as EST with mechanical lithotripsy (ML) for the removal of large CBD stones, and EPLBD was associated with fewer complications. Although this was a well-designed prospective randomized study, it was stopped before reaching full enrollment because the interim analysis showed a significant difference in postendoscopic retrograde cholangiopancreatography (ERCP) cholangitis in favor of patients subjected to EPLBD. Thus, there is a substantial possibility of a type II error. Also, the comparison of cost-effectiveness for complete stone removal and recurrence rate of choledocholithiasis between the two methods was not mentioned. Therefore, the aim of this study was to evaluate the efficacy of EPLBD for preventing recurrence of choledocholithiasis in comparison with EST and analyze the cost-effectiveness for removal of large CBD stone between EPLBD and EST. Furthermore, we investigated the risk factors predicting recurrence of biliary stones.

MATERIALS AND METHODS

1. Patients

A total of 1,580 patients who underwent endoscopic biliary stone extraction at Seoul National University Hospital from January 2001 through July 2010 were retrospectively reviewed. Eligible patients for this study were defined as the followings: 1) choledocholithiasis was treated by EPLBD with minor EST or EST with ML, 2) follow-up period more than 9 months after complete stone removal. A total of 90 patients treated for their large CBD stones by EPLBD or EST with ML were finally enrolled in this study. Endoscopic and fluoroscopic findings, laboratory results, procedure-related complication rate and recurrence rate of choledocholithiasis were compared according to different type of technical approaches for the removal of CBD stones. This study protocol was approved by the institutional review board of Seoul National University Hospital.

2. Endoscopic procedures

ERCP was performed with standard side-viewing duodenoscopes (TJF-200, TJF-240, and TJF-260; Olympus, Tokyo, Japan) under conscious sedation with midazolam (2 to 5 mg) and meperidine (25 to 50 mg). After CBD stones were identified with cholangiogram, EST with standard pull-type papillotome was performed according to the standard technique (Fig. 1). The size and extent of EST was done with discretion of attending endoscopist. Supplementary EPLBD was done if stone size was too large to extract through biliary orifice or discrepancy of stone size and distal bile duct diameter was present. Balloon dilation was then performed with CRE™ wire-guided balloon dilator (Boston Scientific, Natick, MA, USA) with maximum sizes of 12, 15, 18, or 20 mm placed across the papilla among the patients with minor EST. The balloon was gradually inflated with diluted contrast medium until it was estimated to be of adequate size to allow for stone removal under endoscopic and fluoroscopic control. The inflation was maintained for 30 to 60 seconds after the balloon reached an appropriate size. The maximal diameter of

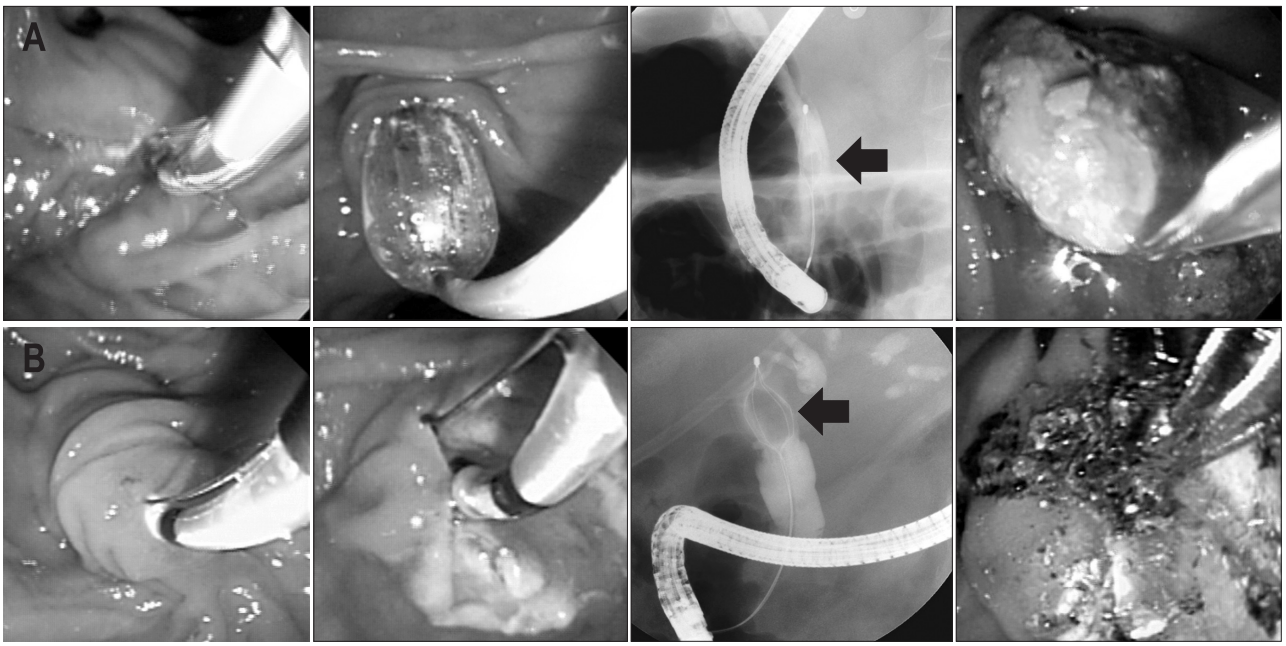

Fig. 1. Endoscopic and radiologic views of biliary stone removal by (A) endoscopic papillary large balloon dilation with minor endoscopic sphincterotomy and (B) endoscopic sphincterotomy with mechanical lithotripsy. The arrow indicates common bile duct stones.

balloon did not exceed the maximal diameter of CBD to prevent perforation. EPLBD without EST was avoided due to the risk of extensive perforation or pancreatitis. Although it is still controversial that partial EST before EPLBD is necessary, minor EST before balloon dilation might decrease the risk of pancreatitis since EST prior EPLBD results in separation between pancreatic and biliary orifices, and the force exerted by the dilating balloon is directed more toward the bile duct than the pancreatic orifice after EST.[5,6] Another advantage of minor EST before EPLBD is direct observation of the remaining intact papillary roof during gradual balloon inflation, which can help to avoid perforation.[20]

If stone clearance could not be achieved using stone extraction baskets and/or stone retrieval balloons, the stones were fragmented using ML. Complete stone removal was documented by the absence of any filling defect with a final cholangiogram. Biliary stent or nasobiliary tube was placed if complete stone removal was not achieved, and repeated ERCP was done until complete stone removal. Complications during ERCP and other relevant endoscopic findings such as periampullary diverticula were recorded in detail. Bleeding was defined by clinical parameters and by decision of clinicians not just by endoscopic evidence of bleeding. Post-ERCP pancreatitis was diagnosed on the basis of new onset or worsening abdominal pain and an increase of serum amylase and lipase levels at least three times greater than the normal upper limit, within 24 hours after procedure. Post-ERCP cholangitis was diagnosed on the basis of increased body temperature (>38°C) over 24 hours with abdominal pain. Perforation was defined by the presence of free air or contrast leakage in radiologic exams as well as clinical course of the patients. Severity of each complication was evaluated using established consensus criteria.[21]

3. Estimation of physical findings of CBD stone and cost of medical expenses

Stone size and number were documented on cholangiogram during the initial ERCP. Maximal diameter of biliary stone and CBD were measured from the relation of the diameter of duodenoscope on cholangiogram.

The total cost for the treatment of choledocholithiasis was defined as the sum of the cost of ERCP, EST, ML, EPLBD, and biliary stent. Each price of the procedures (including device fee) and devices were approximated: ERCP $224, repeat ERCP within 15 days $113, guide wire $118, EST $227, ML $397, trapezoid basket $231, EPLBD $313, EPBD $186, stone extraction basket $256, stone retrieval balloon $166, and biliary plastic stent $47.

4. Follow-up

Follow-up after initial ERCP was based on outpatient clinic. Additional work-ups such as computed tomography and/or ERCP were done if it was necessary with recurrence of symptoms or signs. Recurrence of choledocholithiasis was defined as newly detected CBD stones on images taken at least 6 months apart from the complete removal of previous CBD stones.

5. Statistical analysis

Categorical and binary variables were tested using chi-square test or Fisher exact test according to the treatment. Student t-test or Mann-Whitney U test were used for continuous variables. Recurrence was compared using Kaplan-Meier method with log-rank test. Potential risk factors for stone recurrence were initially assessed by univariate analysis. Multivariate analysis was performed on factors with associated p-values of <0.25 by univariate analysis and Cox proportional hazard model was used in multivariate analysis to identify independent factors associated with recurrence. Data are presented as mean±standard error of the mean or median (range) wherever appropriate. A $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

The median age of study patients was 69 years old (range, 38 to 92 years old) at the time of initial diagnosis, and there were 45 males and 45 females (Table 1). Successful removal of CBD stone was achieved in 49 patients using EPLBD and in 41 patients using EST with ML. Female was significantly predomi-

Table 1. The Baseline Characteristics of the Patients

Characteristic	Endoscopic papillary large balloon dilation (n=49)	Endoscopic sphincterotomy (n=41)	p-value
Age, yr	68 (38–92)	72 (49–89)	0.28
Gender, male/female	31/18	14/27	0.006
Median follow-up, mo	48 (12–87)	33 (10–130)	0.29
Initial bilirubin, mg/dL	3.9±0.8	3.7±0.7	0.59
Initial ALP, IU/L	246±40	264±45	0.72
Stone diameter, mm	16.5±0.9	16.8±0.8	0.80
Stone no.	2 (1–14)	3 (1–25)	0.26
Impacted stone	9 (18)	8 (20)	0.89
Duct diameter, mm	20.9±0.7	20.7±0.9	0.90
Periampullary diverticula	20 (41)	17 (41)	0.95
Lithotripsy	14 (29)	41 (100)	<0.001
Biliary endoprosthesis	10 (20)	21 (51)	0.002
Early complications	4 (8)	4 (10)	>0.99
GB status			0.24
Acalculous GB	15 (31)	13 (32)	
Calculous GB	11 (22)	15 (36)	
Prior cholecystectomy	23 (47)	13 (32)	

Data are presented as median (range), mean±SEM or number (%).
ALP, alkaline phosphatase; GB, gallbladder.

Table 2. The Results of the Treatment Procedures for Large Common Bile Duct Stones

	Endoscopic papillary large balloon dilation (n=49)	Endoscopic sphincterotomy (n=41)	p-value
Lithotripsy	14 (29)	41 (100)	<0.001
Biliary endoprosthesis	10 (20)	21 (51)	0.002
Early complications	4 (8)	4 (10)	>0.99

Data are presented as number (%).

nant in EPLBD group compared to EST with ML group. There was no significant difference in size and number of stones and maximal diameter of CBD between the two groups (EPLBD vs EST groups). ML was more frequently performed in EST group (41 patients) than in EPLBD group (14 patients): 100% versus 29%; p=0.001 (Table 2). Among EPLBD group, 14 patients who underwent ML had significantly larger biliary stones than rest of 35 patients who did not (21.6±1.3 mm vs 14.5±0.9 mm; p<0.001). Endoscopic biliary stent was more frequently placed in EST group compared to EPLBD group (51% vs 20%; p=0.002).

There was no treatment related mortality and there were eight patients (9%) who experienced minor procedure-related adverse events. There were four patients with complications in EPLBD (8%) and in EST (10%) group each and the complication rate was not significantly different between the two groups (p>0.99): three minor bleeding in EPLBD group, three acute pancreatitis in EST group, one acute cholangitis in EPLBD group and one CBD perforation in EST group. Bleeding was more common in EPLBD group (6% vs 0%; p=0.25), whereas post-ERCP pancreatitis occurred more common in EST group (7% vs 0%; p=0.09). All the procedure-related adverse events were improved after conservative management.

Complete stone removal at first ERCP session was achieved in 62 patients (69%): 38 patients (78%) in EPLBD group and 24 patients (59%) in EST group (p=0.05). There were 11 patients (22%) who required repeated sessions of ERCP for complete removal of CBD stones in EPLBD group: twice in eight patients and three times in three patients. On the other hand, there were 17 patients (41%) who required repeated sessions of ERCP for complete removal of CBD stones in EST group: twice in nine patients, three times in six patients, four times in one patient and seven times in one patient. Repeated sessions of ERCP were significantly required in EST group than in EPLBD group to achieve complete removal of biliary stones (1.7±0.2 times vs 1.3±0.1 times; p=0.03). The cholecystectomy was done in eight patients (31%) among 26 patients with calculous gallbladder after CBD stone removal.

Choledocholithiasis recurred in 26 patients (29%) during median follow-up of 45.1 months (range, 10.2 to 129.5 months): 15 patients (31%) and 11 patients (27%) in EPLBD and EST

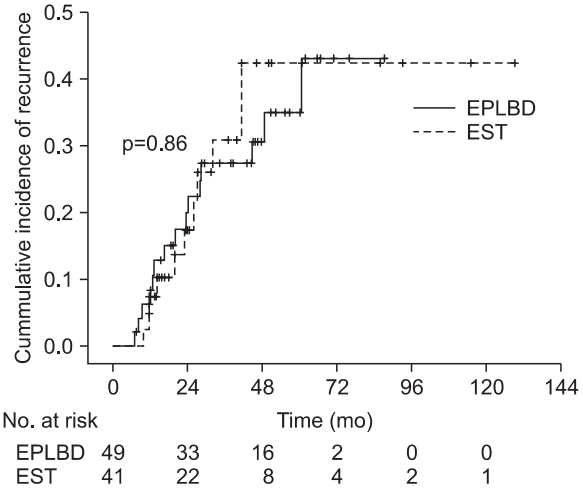

Fig. 2. Cumulative incidence of biliary stone recurrence. Kaplan-Meier estimates of the rate of patients with recurrence in the endoscopic papillary large balloon dilation (EPLBD) and endoscopic sphincterotomy (EST) groups (p=0.86 by log-rank test).

group respectively, and there was no statistically significant difference in cumulative incidence of recurrences (p=0.86) (Fig. 2). Interestingly, maximum diameter of recurred stone during follow-up period tended to be larger after EST than after EPLBD (16.4±1.9 mm vs 13.4±1.1 mm; p=0.18). Therefore, four patients in EST group eventually underwent EPLBD for recurred stone removal. In addition, most of the recurred stones always have been brown pigmented in both groups (87% in EPLBD and 100% in EST, p=0.49). The total number of recurrences during follow-up period was also higher after EST without significant difference (1.9±0.5 vs 1.3±0.2; p=0.31).

The mean amount of costs required for the complete stone removal per patient was significantly higher in EST group than in EPLBD group (USD $1,644 vs $1,225; p=0.04). Besides, costs for the treatment of recurrent biliary stones were $947 and $1,684 in EPLBD and EST group, respectively (p=0.19).

Possible risk factors related with biliary stone recurrence, including age, gender, largest diameter and number of stone, stone impaction, CBD diameter, periampullary diverticula, EPLBD, lithotripsy, biliary endoprosthesis, early complication, and gallbladder status were evaluated (Table 3). CBD diameter was the only significant factor predicting recurrent biliary stones among the above variables. The recurrence rate was 40% when the maximum CBD diameter was more than 20 mm, whereas the recurrence rate was 18% when the maximum CBD diameter was 20 mm or less than 20 mm (p=0.03). Multivariate analysis was done with the following factors: number of stone, size of stone, lithotripsy and biliary endoprosthesis. The most significant factor associated with recurrent biliary stones was dilation of CBD (relative risk, 1.09; 95% confidence interval, 1.02 to 1.17; p=0.02) (Table 4).

Table 3. The Prognostic Factors Affecting Stone Recurrence (by Univariate Analysis)

Factor	No.	Recurrence	RR (95% CI)	p-value
Age, yr				0.53
≤70	46	13	1	
>70	44	13	1.28 (0.59–2.77)	
Gender				0.61
Male	45	12	1	
Female	45	14	1.23 (0.57–2.65)	
Stone diameter, mm				0.26
≤15	33	8	1	
>15	57	18	1.62 (0.70–3.73)	
Stone no.				0.22
1	30	7	1	
≥2	60	19	1.70 (0.71–4.07)	
Impacted stone				0.93
Absent	73	21	1	
Present	17	5	1.05 (0.39–2.79)	
Diameter of common bile duct, mm				0.03
≤20	45	8	1	
>20	45	18	2.42 (1.05–5.56)	
Periampullary diverticula				0.88
Absent	53	16	1	
Present	37	10	1.06 (0.48–2.34)	
Endoscopic papillary large balloon dilation				0.86
No	41	11	1	
Yes	49	15	0.93 (0.43–2.04)	
Lithotripsy				0.15
No	35	8	1	
Yes	55	18	1.83 (0.79–4.23)	
Biliary endoprosthesis				0.21
No	59	16	1	
Yes	31	10	1.65 (0.74–3.68)	
Early complications				0.37
No	82	25	1	
Yes	8	1	0.41 (0.06–3.04)	
GB status				0.37
Cholecystectomy or acalculous GB	72	20	1	
Calculous GB without cholecystectomy	18	6	1.53 (0.61–3.85)	

RR, relative risk; CI, confidence interval; GB, gallbladder.

Table 4. The Prognostic Factors Affecting Stone Recurrence (by Multivariate Analysis)

Variable	RR (95% CI)	p-value
Stone no. (≥2)	1.67 (0.68–4.08)	0.26
Duct diameter	1.09 (1.02–1.17)	0.01
Lithotripsy	1.24 (0.51–3.02)	0.63
Biliary endoprosthesis	1.73 (0.72–4.13)	0.22

RR, relative risk; CI, confidence interval.

DISCUSSION

It has been very well known that recurrent biliary stone is the most common late complication after biliary stone removal with EST or EPLBD.[1] However, there are few studies comparing recurrence rate of biliary stones according to the techniques (EPLBD and EST) used for removal of large CBD stones. We have assumed that EPLBD would have somewhat advantage over EST to prevent recurrent biliary stones because EPLBD does not cut and ablate sphincter muscle like EST at the beginning of this study. However, the results of this study showed that EPLBD was not superior to EST for the prevention of biliary stone recurrence. On the other hand, EPLBD can be preferred in terms of requiring less session of repeated ERCPs compared to EST, and ultimately EPLBD was more cost-effective in the end. The recent randomized trial comparing EPLBD with EST also showed that the overall cost was significantly reduced in EPLBD group.[22] The size of recurrent stone was also larger in EST group without significant differences, and it may be due to the small number of patients with a recurrence as a whole.

Small CBD stones can be easily extracted after EPBD, whereas large stones are hard to extract and often need ML.[23] Thus, we can easily expect that the most patients who underwent EPLBD or ML have large biliary stones. In that reason, it can be said that the size of CBD stones are similar between EPBLD and EST with ML groups. Therefore, we compared the recurrence rate between the two groups using EPLBD or EST with ML to remove CBD stones. As we expected, there was no significant difference in the maximum diameter of CBD stone between the two groups and we could truly compare the recurrence rate between the two groups.

Biliary endoprosthesis was done in 31 patients at initial ERCP and it was more significantly frequent in EST group compared to EPLBD group (51% vs 20%; p=0.002). This result showed another aspect that there were more residual stones in EST with ML group and obviously EST group required multiple sessions of repeated ERCPs to achieve complete removal of CBD stones. There were 14 patients (29%) who underwent additional ML to remove CBD stones in EPLBD group and their mean diameter of CBD stone was greater than 20 mm. Also, the authors would like to mention that we have policies not to use diameter larger than 20 mm during EPBLD procedure in our institution. Therefore, they were treated with ML after EPLBD. Since we compared EPLBD versus EST with ML for removal of large CBD stones, it is hard to convince that EPLBD reduces the need for ML for removal of large stones based on the results of this

study. However, only 29% of patients in EPLBD group required ML and this finding is in consistent with previous randomized trial.[22]

The early complication rate after EPLBD is known to be around 4% to 14% and it was 8% in this study which was in accordance with previous report.[7,8,24,25] In addition, EST is known to carry an 8% to 12% risk of early complications,[3] and we found that ours was 10%. Bleeding was the most common complication occurred 6% of patients after EPLBD, whereas there was no post-ERCP pancreatitis after EPLBD. While pancreatitis was an early concern with EPLBD, the rates have proven to be low and recent study suggested that direct physical compression by large size balloons is not a major factor in the etiology of pancreatitis following EPLBD.[10] Adequate dilation of the papilla with EPLBD may reduce the trauma to the papilla during stone removal, which results in lower incidence of pancreatitis. Another reason of no post-ERCP pancreatitis in EPLBD group is that minor EST was always done before EPLBD in our study. It has been reported that minimal EST before LBD decreases the risk of pancreatitis.[5] Conversely, post-ERCP pancreatitis was more common in EST group since every patient in EST group underwent ML in present study. ML may trigger papillary edema or spasm that may obstruct the pancreatic duct orifice.[26,27]

Bile duct stones most commonly have their origin in the CBD as primary stones rather than in the gallbladder with secondary descent into the bile duct.[28] Also, most of the recurred stones in this study were brown pigment stones which represent formation of stones in the CBD due to bile infection by duodenobiliary reflux.[17,29,30] Thus, there was no significant difference of stone recurrence regardless of cholecystectomy.

The incidence of biliary stone recurrence during follow-up was 29%, which was higher than previous studies.[1,31,32] It may be due to patients with large biliary stones were enrolled in present study. ML was performed in 55 patients (61%) and there was a possibility of remnant small stone fragments after ML may act as a nidus for recurrent stones.[33] Besides, it could be thought that the migrating stones from gallbladder might increase the recurrence rate. However, there was no significant difference in stone recurrence according to the status of gallbladder in present study.

CBD dilation was the single most significant factor associated with recurrence of CBD stones in multivariate analysis and this result was in consistent with previous reports.[16,34] A dilated CBD results in bile stasis and bacterial infection, which play an essential role in the formation of pigment stones.[29,30,34] In addition, it is possible that small fragmented stones were more likely to be missed with cholangiogram in patients with a dilated CBD.[16]

The main limitation of our study was the retrospective data collection and analyses. However, we compared the patients who underwent EPLBD with the patients who underwent EST and ML to minimize the discrepancy of stone natures between the two groups. The other limitation was that relatively small number of patients was enrolled in this study. However, follow-up of patients with choledocholithiasis is difficult because most patients become free from symptoms after stone removal and leave medical institutions. We had performed endoscopic biliary stone extraction in 1,580 patients during almost 10 years and begun to perform EPLBD for stone removal since 2004. However, only 90 patients could be enrolled in this study due to lack of follow-up. In the future, long-term follow-up study with CBD stone cohort will be required to identify the efficacy of EPLBD for prevention of recurrent stones and the risk factors of stone recurrence after EPLBD.

We could find out that EPLBD was not superior to EST for prevention of recurrent biliary stones and dilated CBD was the only significant factor predicting the recurrence of CBD stones. Here, we would like to address that EPLBD is the better treatment of choice than EST to remove large CBD stones since EPLBD required less number of ERCP sessions with cheaper costs. Further investigations with larger number of patients in prospective studies would give us more insights to figure out the best management in treatment of patients with large CBD stones.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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