REVIEW

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Endoscopic Papillary Balloon Dilation for Removal of Choledocholithiasis: Indications, Advantages, Complications, and Long-Term Follow-Up Results

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Endoscopic papillary balloon dilation (EPBD) is an alternative method of endoscopic sphincterotomy (EST). Although concerns regarding post-procedure pancreatitis have been expressed, EPBD has come to be recognized as an effective and safe method for stone removal in specific cases. To analyze the proper indications, ideal methods, complications, and long-term follow-up results for EPBD, we reviewed articles about EPBD located through a search of the PubMed data base. We analyzed the ballooning methods, indications, results and complications of EPBD among the articles found and compared the results with those of EST. We considered the authors' own clinical experience and knowledge in developing recommendations for EPBD. EPBD showed similar efficacy and safety for the removal of choledocholithiasis to that of EST. Although large or multiple stones were difficult to remove by EPBD, it was safer and easier to apply in patients with coagulopathy or abnormal anatomy. To prevent severe pancreatitis, excessive ballooning and impractical cannulation should be avoided, and precut sphincterotomy or adjuvant prophylaxis should be considered. Due to its preservation of the sphincter of Oddi, EPBD is expected to have fewer long-term complications, such as stone recurrence, cholangitis and cholecystitis. In conclusion, EPBD appears to be safe and effective for the treatment of choledocholithiasis with proper selection of ballooning methods and patients. **(Gut Liver 2011;5:1-14)**

Key Words: Choledocholithiasis; Endoscopic papillary balloon dilation; Endoscopic sphincterotomy; Endoscopic papillary large balloon dilation

INTRODUCTION

Before endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy was introduced in the 1970s, there was no other choice than surgery for the treatment of choledocholithiasis except. After Classen *et al*.[1] and Kawai *et al*.[2], first introduced endoscopic sphincterotomy (EST), the endoscopic removal of stones has been widely accepted as a standard treatment for bile duct stones. Moreover, advances in intraductal lithotripsy techniques, such as mechanical basket lithotripsy and electrohydraulic lithotripsy, have made it easier to fragment large stones. Although the safety of EST has been proven in many studies, there are still several limitations on its applications due to complications: pancreatitis (5.4%), hemorrhage (2.0%), perforation (0.3%), cholangitis (1.0%), cholecystitis (0.5%), and procedure-related death (0.4%).[3] Bleeding after EST should be carefully monitored in patients with coagulopathy because of its high mortality (24.3-22.2%).[4-6] Recurrence of stones and chronic biliary inflammation were also associated with loss of ampulla of Vater function.[7-9] There have been many efforts to decrease the occurrence of these complications as much as possible.

Endoscopic papillary balloon dilation (EPBD) is almost the only existing alternative to EST. Although it was not welcomed in Western groups because of complications, it has come into wide usage in Korea and Japan. Nowadays, an extended technique of EPBD, endoscopic papillary large balloon dilatation (EPLBD) with limited sphincterotomy, is successfully used for stone removal.

To maximize the effects and minimize the complications of endoscopic lithotripsy, it is important to recognize the proper indications and to apply the technique in a proper manner. In this paper, we reviewed articles about EPBD by searching PubMed for making suggestions on the appropriate use of EPBD. We analyzed the ballooning methods, indications, results and complications of EPBD among the articles, and compared the results with those of EST. We considered the authors' own

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clinical experience and knowledge in developing recommendations for EPBD.

EPBD

EPBD was presented for the first time by Staritz *et al*.[10], in order to minimize damage to the sphincter of Oddi. Following selective deep cannulation, the balloon catheter was placed across the papillary orifice and gradually inflated with diluted contrast material at a pressure of 8-12 atm. The sphincter was adequately dilated if the waist in the balloon completely disappeared. The fully inflated balloon was maintained in its position for dozens of seconds, and then deflated. The procedure can be repeated for complete dilation. Various sizes of balloon catheter with 6-15 mm in diameter and 30-40 mm in length can be used according to the bile duct diameter and stone size. The velocity and duration of balloon inflation varied from seconds to minutes. After EPBD, the stones were extracted using a Dormia basket and/or a retrieval balloon catheter (Fig. 1).

1. Advantages

1) EPBD has several advantages over EST

First, it is less traumatic to the ampullary sphincter, which was proven in both animal and human studies. The resected specimens of pigs, obtained immediately after EPBD, showed only acute inflammation and intramucosal hemorrhage without smooth muscle disruption on histological analysis.[11] Even after several weeks, no architectural distortion or smooth muscle disruption was noted. In human studies, histological analysis of the papilla after EPBD showed only mild to moderate inflammation and fibrosis in most patients (80-90%), while no smooth muscle disruption nor architectural distortion was observed.[12,13]

Second, EPBD may preserve papillary function. After EPBD, a mild decrease in papillary function was noted on manometry without significant difference. On the other hand, all patients who had received EST completely lost papillary function.[14] Papillary function began to return to normal only a month after EPBD, and the basal and peak pressures of the sphincter of Oddi (SO) had significantly recovered by that time as compared with the data immediately after EPBD.[15] In contrast, SO contraction did not recover even after one year after EST.[16] Because the cutting method was unnecessary, the SO function was not completely lost after EPBD.

Third, EPBD was shown to be safer for patients with bleeding tendency. Coagulopathy under liver cirrhosis, portal hypertension or administration of anticoagulation is a known risk factor for EST-related bleeding.[3,17] Because EPBD can avoid an incision, it may significantly reduce the bleeding risk and mortality in patients with liver cirrhosis and coagulopathy.[18-20]

Finally, it is favorable for those with abnormal anatomy, such as periampullary diverticulum and Billroth II gastrojejunostomy. EST is technically difficult in patients with periampullary diverticulum or Billroth II gastrojejunostomy because the cutting direction of the sphincterotome is not easy to control. Therefore

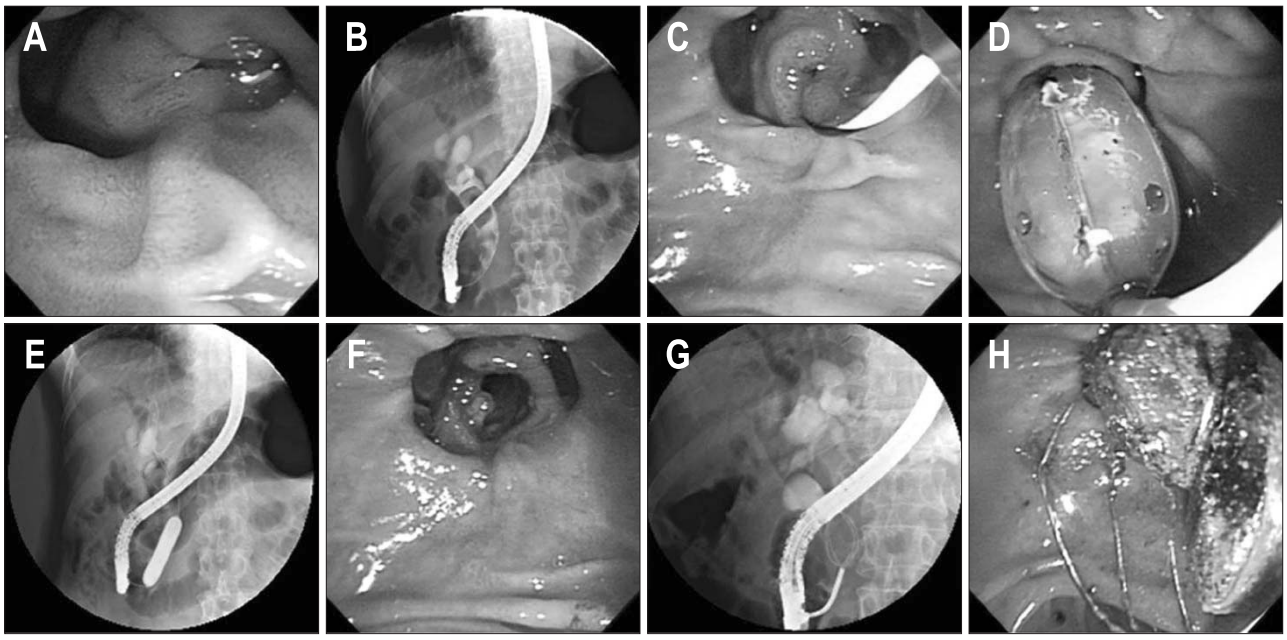

Fig. 1. Endoscopic papillary balloon dilation (EPBD) for choledocholithiasis with perivater diverticulum. (A) Duodenoscopic finding shows an ampulla of Vater located in a diverticulum. (B) ERCP shows multiple stones in the common bile duct. (C) The guidewire is inserted into the bile duct. (D) The 10 mm balloon is gradually inflated with diluted contrast material; inflation is maintained for 30 seconds. (E) X-ray during balloon dilation shows complete disappearance of the sphincter waist. (F) Duodenoscopic finding after EPBD shows a well-visualized common bile duct with a large dilated opening of the sphincter of choledochus. (G) ERCP shows a stone grasped by a mechanical lithotripter. (H) Duodenoscopic finding shows stones removed from the common bile duct by a Dormia basket.

Table 1. Comparisons between EPBD and EST for Removal of Choledocholithiasis

Authors (published yr)	Group	Patients' factors				Procedure			Results		Complications
		Age, yr	Sex, M/F	Stone no.	Stone size, mm	Balloon size, mm	Ballooning method	Mechanical lithotripsy, No. (%)	Complete ratio at first session, No. (%)	Complete ratio at the end of session, No. (%)	
Minami *et al.*[14] (1995)	EPBD (n=20)	64.0±11.2 (38-82)	13/7	-	-	8	15-20 psi for 180 sec	-	-	20 (100)	Pancreatitis 2 (10.0%) Biliary infection 0
	EST (n=20)	71.3±14 (44-83)	9/11	-	-	-	-	-	-	20 (100)	Pancreatitis 2 (10.0%) Biliary infection 0
Bergman *et al.*[24] (1997)	EPBD (n=101)	72 (27-98)	43/58	2 (1-14)	10 (3-36)	8	Inflation for 60-120 sec Maintain for 45-60 sec	31 (30.7) >10 mm	81 (80.0)	90 (89.0)	Pancreatitis 7 (6.9%) Biliary infection 4 (4.0%) Perforation 2 (2.0%) Bleeding 0 Mortality 1 (1.0%)
	EST (n=101)	71 (29-96)	45/56	1 (1-15)	9 (4-27)	-	-	13 (12.9)	92 (91.0)	92 (91.0)	Pancreatitis 7 (6.9%) Bleeding 4 (4.0%) Biliary infection 5 (5.0%) Perforation 1 (1%) Mortality 0
Ochi *et al.*[46] (1999)	EPBD (n=55)	62.6±15.9 (24-87)	34/21	2.1±1.9	8.1±3.4	8	8 atm Maintain for 60 sec two times	7 (13.7)	40* (78.5)	51 (92.7)	Pancreatitis 0 Perforation 0 Biliary infection 0
	EST (n=55)	66.3±14.3 (21-89)	31/24	1.7±1.2	8.8±4.2	-	-	2 (3.7)	51* (94.4)	54 (98.1)	Pancreatitis 2 (3.6%) Perforation 1 (1.9%) Biliary infection 0
Arnold *et al.*[23] (2001)	EPBD (n=30)	54.2 (23-85)	11/19	1.6±1.1	7±3.5	8	10 atm (1010 kP) for 60 sec two times	-	23 (77.0)	23 (77.0)	Pancreatitis 6 (20.0%) Biliary infection 3 (10.0%) Bleeding 0
	EST (n=30)	58.5 (22-94)	13/17	1.8±1.5	10±4.7	-	-	-	30 (100)	30 (100)	Pancreatits 3 (10.0%) Biliary infection 0 Bleeding 2 (6.7%)
Yasuda *et al.*[16] (2001)	EPBD (n=35)	69.5 (42-86)	16/19	3.7 (1-16)	12.4 (4-24)	8	6 atm for 60 sec two times	17 (48.6) >11 mm	-	35 (100)	Pancreatitis 2 (5.7%) Biliary infection 1 (3.7%) Bleeding 0 Perforation 0
	EST (n=35)	69.4 (43-88)	21/14	3.3 (1-16)	12.3 (5-24)	-	-	9 (25.7) >20 mm	-	35 (100)	Pancreatitis 2 (5.7%) Biliary infection 1 (3.8%) Bleeding 0 Perforation 0

Table 1. Continued

Authors (published yr)	Group	Patients' factors				Procedure			Results		Complications
		Age, yr	Sex, M/F	Stone no.	Stone size, mm	Balloon size, mm	Ballooning method	Mechanical lithotripsy, No. (%)	Complete ratio at first session, No. (%)	Complete ratio at the end of session, No. (%)	
Natsui *et al.*[25] (2002)	EPBD (n=70)	64.5 (23-87)	33/37	2.7 (1-15)	9.2 (3-22)	8	8 atm for 120 sec	29 (41.4)	41 (58.6)	65 (92.9)	Pancreatitis 4 (5.7%) Biliary infection 2 (2.9%) Bleeding 0 Perforation 0
	EST (n=70)	67.1 (38-88)	33/37	2.6 (1-15)	9.7 (3-17)	-	-	27 (38.6)	49 (70.0)	69 (98.6)	Pancreatitis 3 (4.3%) Biliary infection 3 (4.3%) Bleeding 2 (2.9%) Perforation 0
Vlavianos *et al.*[59] (2003)	EPBD (n=103)	60.8 (56.8-64.7)	25/78	≥3, 40 (39%)	≤5 (26%) 6-9 (36%) ≥10 (38%)	10	12 atm for 30 sec	7 (6.8)	65 (63.1)	90 (87.4)	Pancreatitis 5 (5.0%) Biliary infection 2 (2.0%) Mortality 0
	EST (n=99)	61.9 (58.3-65.4)	35/64	≥3, 25 (25%)	≤5 (31%) 6-9 (26%) ≥10 (42%)	-	-	11 (11.1)	63 (63.6)	86 (86.9)	Pancreatitis 1 (1.0%) Biliary infection 1 (1.0%) Mortality 1 (1.0%)
Fujita *et al.*[37] (2003)	EPBD (n=138)	66.8 (26-93)	75/63	2.4±2.9	7.0±3.1	8	Inflation for 180 sec Maintain for 15 sec	20 (14.5)	105 (78.9)	137 (99.3)	Pancreatitis 15 (10.9%) Biliary infection 2 (1.4%) Bleeding 0 Perforation 0
	EST (n=144)	68.4 (31-93)	92/52	2.4±2.5	7.3±3.4	-	-	17 (11.8)	113 (79.0)	144 (100)	Pancreatitis 4 (2.8%) Biliary infection 6 (4.2%) Bleeding 2 (1.4%) Perforation 0

Table 1. Continued

Authors (published yr)	Group	Patients' factors				Procedure			Results		Complications
		Age, yr	Sex, M/F	Stone no.	Stone size, mm	Balloon size, mm	Ballooning method	Mechanical lithotripsy, No. (%)	Complete ratio at first session, No. (%)	Complete ratio at the end of session, No. (%)	
Lin *et al.*[26] (2004)	EPBD (n=51)	64 (28-90)	28/23	≥3 20 (39%)	0.8±0.6	8-12	3-8 atm for 120 sec	1 (2.0)	41 (86.3)	48 (94.1)	Pancreatitis 0 Bleeding 1 (2.0%) Biliary infection 0 Perforation 0
	EST (n=53)	65 (28-88)	31/22	≥3 28 (53%)	0.8±0.6	-	-	2 (3.8)	47 (88.7)	53 (100)	Pancreaittis 0 Bleeding 14 (26.4%) Biliary infection 0 Perforation 0
Disario *et al.*[35] (2004)	EPBD (n=117)	47±19	41/76	1 (1-100)	6 (0.5-10)	8	120 sec	-	-	114 (97.4)	Pancreatitis 12 (10.3%) Biliary infection 1 (0.9%) Bleeding 11 (10.5%) Perforation 0 Mortality 2 (1.7%)
	EST (n=120)	54±19	31/89	1 (1-100)	5 (0.5-14)	-	-	-	-	111 (92.5)	Pancreatitis 1 (0.8%) Biliary infection 1 (0.8%) Bleeding 32 (27%) Perforation 1 (0.8%) Mortality 0
Tanaka *et al.*[27] (2004)	EPBD (n=16)	67.2 (50-78)	10/6	2.0 (1-12)	10.2±3.5 (5-15)	8	8 atm for 120 sec	8 (50)	11 (68.8)	16 (100)	Pancreatitis 3 (18.8%) Biliary infection 0 Bleeding 0 Perforation 0
	EST (n=16)	70.6 (49-87)	13/3	2.0 (1-4)	12.4±6.0 (4-23)	-	-	6 (37.5)	9 (56.2)	16 (100)	Pancreatitis 3 (18.8%) Biliary infection 2 (12.5%) Bleeding 0 Perforation 0
Toda *et al.*[28] (2005)	EPBD (n=94)	68.5 (24-92)	48/46	1.9 (1-15)	10 (2-30)	8	8 atm for 120 sec	-	23 (26.1)	88 (93.6)	Pancreatitis 7 (6.4%) Biliary infection 4 (4.2%) Bleeding 0 Perforation 0
	EST (n=102)	68 (27-96)	54/46	2 (1-10)	12 (2-40)	-	-	-	34 (34.0)	88 (88.0)	Pancreatitis 3 (3%) Biliary infection 6 (6%) Bleeding 2 (2.0%) Perforation 2 (2.0%)

Table 1. Continued

Authors (published yr)	Group	Patients' factors: Age, yr	Sex, M/F	Stone no.	Stone size, mm	Procedure: Balloon size, mm	Ballooning method	Mechanical lithotripsy, No. (%)	Results: Complete ratio at first session, No. (%)	Complete ratio at the end of session, No. (%)	Complications
Liao *et al.*[29] (2008)	EPBD† (n=35)	72±13.0	17/18	13/22	10.0±6.1	10	Slow inflation 6 atm Maintain for 60 sec	8 (22.9)	32 (91.4)	35‡ (100)	Pancreatitis 2 (5.7%) Biliary infection 1 (2.9%) Bleeding 0
	EST† (n=25)	70.8±14.0	16/9	12/13	11.1±5.1	-	-	10 (40)	19 (76.0)	21‡ (84.0)	Pancreatitis 3 (12.0%) Biliary infection 2 (8.0%) Bleeding 2 (8.0%)
	EPBD§ (n=11)	62.7±17.3	7/4	3/8	9.1±5.4	10	Slow inflation 6 atm Maintain for 60 sec	4 (36.4)	10 (90.9)	11 (100)	No complication
	EST§ (n=9)	69.8±16.2	3/6	4/5	10.8±4.8	-	-	1 (11.1)	9 (100)	9 (100)	No complication

Biliary infection included cholangitis and cholecystitis.
EPBD, endoscopic papillary balloon dilation; EST, endoscopic sphincterotomy.
*p=0.02; †In the patients with periampullary diverticulum; ‡p=0.026; §In the patients with prior sphincterotomy history.

a high level of precision in the direction and length of the incision is necessary to avoid severe complication. In contrast, EPBD requires simple technique to insert the balloon catheter into the common bile duct and inflate it. Therefore, EPBD is more suitable for the patients with periampullary diverticulum or Billroth II gastrojejunostomy.[21] Komatsu *et al.*[20] reported on their experience of EPBD in 226 patients, and EPBD was successful in 86 patients (38.0%) with periampullary diverticulum and in two patients who had previously undergone Billroth II gastrectomy.

2. Comparison of success rates between EPBD and EST for removal of choledocholithiasis (Table 1)

There have been many trials comparing the efficacy and safety of EPBD with EST. According to the meta-analysis of eight randomized, controlled studies, the overall success rate for stone removal was similar in the two groups (94.3% vs 96.5%, p=0.2), but the completion rate for the first session was significantly higher in the EST group than in the EPBD group (79.8% vs 70.0%, p=0.001).[22] Mechanical lithotripsy was also needed significantly more often in the EPBD group in that study (20.9% vs. 14.8%, p=0.01). In 23% of patients who had failed stone removal with EPBD at the first session, the additional EST as a rescue procedure contributed to raising the overall success rate of the EPBD group.[23] Another study also showed that 9% of the EPBD group needed the additional EST.[24]

Large or multiple stones are more difficult to remove using EPBD because the biliary opening is not wide enough. The difference of initial success rate between the EPBD and EST group was widened in difficult cases, such as stones of larger than 10 mm in diameter or four or more stones (70.0% vs 83.0%); these cases needed more mechanical lithotripsy in the EPBD group (50.0% vs 23.0%, p<0.01).[24] For patients with stones over 10 mm in diameter, EPBD required a significantly larger mean number of treatment sessions than EST (2.4 vs 1.6, p<0.05).[25] Multiple or larger stones also required the additional EST in13% of patients, while smaller and fewer stones did so in 3% of patients.[24] On the other hand, studies limited to stones smaller than 2.0 cm in diameter showed that not only overall success rate but also initial success rate and requirement of mechanical lithotripsy to be similar in both groups.[26] Tanaka *et al.*[27] also reported that EPBD was more effective in cases with small-sized (≤15 mm) and small numbers (≤3) of stones (100% vs 55.6%, p<0.05). However, Toda *et al.*[28] reported that the initial and overall success rates with EPBD were comparable to that of EST, regardless of stone size.

When EST was difficult to apply due to periampullary diverticulum or prior EST, EPBD was easier and safer than EST.[29]

Table 2. The Causes of Failure of EPBD/EPLBD for Removal of Choledocholithiasis

Authors (published yr)	Failure rate, No. (%)	Causes	
Jeong *et al*.[60] (2009)	9/38* (23.9)	Maximaum transverse diameter of largest stone	0.077 †
		Balloon diameter	0.071 †
		Balloon/stone diameter ratio	0.066 †
Mathuna *et al*.[30] (1995)	22/100 ‡ (22.0) 18/100 § (18.0)	Stone size >15 mm	15.0%
		Intolerance of procedure	2.0%
		Periampullary diverticulum	1.0%
		Situs inversus	1.0%
		Benign distal stricture	1.0%
		Unrecognized retained stones	2.0%
Bergman *et al*.[24] (1997)	20/101 ‡ (20.0) 11/101 § (11.0)	Stone size ≥10 mm or number >3	NE
Heo *et al*.[31] (2007)	17/100 ‡ (17.0)	Stone impaction	NE
	3/100 § (3.0)	Difficulty in accessing the bile duct due to very tortuous CBD and distal BD stricture	
Attasaranya *et al*.[52] (2008)	5/107 ‡ (5.0)	Multiple stones	NE
	5/107 § (5.0)	Large stone (13-30 mm)	
		Broken basket due to hard stone	
		Incomplete stone capture	

EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; NE, not evaluated; CBD, common bile duct; BD, bile duct.
*Application of mechanical lithotripsy or failure to extract stone; † p-value; ‡ Failure at first session; § Overall failure.

3. Causes for failure to remove choledocholithiasis (Table 2)

The maximum diameter of the stones affects complete stone removal, especially when larger than 15 mm in length. Patients' intolerance to the procedure, unrecognized retained stones and anatomic problem such as periampullary diverticulum, situs inversus and benign distal stricture make it difficult to clear stones completely.[30] Tortuous common bile duct and distal bile duct stricture also interfere with accessing the bile duct.[31] In situations where deep cannulation to the bile duct may have failed, precut sphincterotomy was one of the most effective methods. Dilating the balloon immediately after the precut sphincterotomy became the method of choice before EPBD when deep cannulation failed.

4. Complications

1) Post-EPBD pancreatitis

Pancreatitis is one of the most fearful post-ERCP complication, and occurred in 5-19.8% after EPBD.[13,20,30,32,33] Because of the significant occurrence of complications, Kozarek[34] insisted that EPBD should not replace EST. A randomized controlled study was finished prematurely due to excessive morbidity in the EPBD group (20.0% vs 10.0%).[23] Another randomized, controlled multicenter trial was also terminated early at the first interim analysis, because two patients died from severe pancreatitis as a complication of EPBD.[35] Actually, meta-analysis demonstrated that post-ERCP pancreatitis occurred more commonly in the EPBD group than in the EST group (7.4% vs 4.3%, p=0.05).[22] The authors thought that the balloon dilation of the sphincter of Oddi may have been causing spasm, compression and edema of the distal pancreatic duct, resulting in restricted flow of pancreatic juice and causing pancreatitis, biliary obstruction and cholangitis. To minimize the damage on papilla, two different methods of balloon inflation were tried; rapid inflation and maintenance for 120 seconds and slow inflation and maintenance for 15 seconds. However, the incidences of pancreatitis did not differ significantly between the two methods (73.3% vs 60.6%, p=0.3220).[32] A larger balloon (10 to 15 mm) may cause more compression and edema of the distal pancreatic duct, thus precipitating pancreatitis. Smaller balloons of less than 8mm may be safer and more effective in the management of bile duct stones, and decrease the incidence of pancreatitis.[30,36] Balloon dilation in a stepwise fashion, avoiding rapid application and excessive pressure, may also contribute to decreasing the occurrence of the post-EPBD pancreatitis.[37]

According to another study, previous pancreatitis history is one of the most significant factor of EPBD related pancreatitis (odds ratio [OR], 10.69; 95% confidence interval [CI], 1.57-72.97).[36] In contrast, another study revealed that history of acute pancreatitis was not identified as a risk factor, but that contrast medium injection to the pancreas was a significant risk factor by multivariate analysis (OR, 3.788; 95% CI, 1.036-13.853).[32]

As Chinese study showed younger age to be a significant risk factor for post-ERCP pancreatitis (OR, 1.59; 95% CI, 1.06-2.39).[38] The progressive decline in pancreatic exocrine function that comes with aging may protect older patients from pancreatic injury.[39] However, there was no significant difference in the incidence of post-EPBD pancreatitis between older and younger patients.[32,36] However, age of younger than 60 years demonstrated relevance to asymptomatic hyperamylasemia.[36]

Total procedure time, sex, periampullary diverticulum, mechanical lithotripsy, non-dilated bile duct and difficult cannulation were found not to be significant by univariate and multivariate analysis.[32,36] However, cannulation trauma might result in spasm of the sphincter of Oddi and/or hemorrhagic edematous change,[33] and was a potential risk factor for asymptomatic hyperamylasemia after EPBD (OR, 5.12; 95% CI, 2.79-16.81).[36] In cases of difficult cannulation, minimal EST before standard endoscopic balloon dilation may be recommended. Since EST may direct the force exerted by the dilating balloon to be directed more toward the common bile duct than the pancreatic duct, it may decrease the risk of pancreatitis.[40]

Several methods were suggested for preventing EPBD-related pancreatitis. Gabexate mesylate may reduce the incidence of especially moderate or severe pancreatitis.[41] Insertion of a pancreatic stent,[42] epinephrine irrigation after EPBD,[43] isosorbide dinitrate infusion,[44] and injection of botulinum toxin to lower the pancreatic sphincter pressure[45] may augment pancreatic drainage. However these adjuvant interventions also present potential for complications, and their time or cost-effectiveness remains questionable.

2) Bleeding

As stated above, EPBD has little theoretical risk of bleeding, and clinically significant bleeding which was defined as continuous bleeding after procedure or conditions requiring transfusion and additional intervention for hemostasis, is rarely reported after EPBD. Meta-analysis showed no episode of bleeding in the EPBD group, whereas it was noted in 2.0% of the EST group.[22] In case of self-limited or endoscopically controlled bleeding, the incidence was significantly higher in EST group (27%) than in EPBD group (10.5%).[35]

3) Perforation

Although meta-analysis showed no significant difference in the perforation rate between the EPBD and EST groups,[22] only one study reported two retroperitoneal perforations after EBPD,[24] whereas four studies reported five perforations after EST.[24,28,35,46] EPBD does not appear to increase the rate of perforation compared with EST.

4) Abdominal pain during inflation of the balloon

During inflation of the balloon, 23.5-50% of patients felt abdominal pain or discomfort. However this adverse effect was temporary and got better by a reduction in balloon pressure and duration.[20,26,30]

5) Cholangitis and cholecystitis

Acute cholangitis within 15 days after procedure occurred only in the EST group (12.5%).[27] Acute cholecystitis developed more often in the EST group than in the EPBD group (9.9% vs 1.3%, $p<0.05$). This may be explained by loss of sphincter function after EST, which enables bacteria colonization from the intestine into the biliary system.[24]

6) Gallstone ileus

Gallstone ileus is an extremely rare complication of ERCP and EST.[47] Advanced age, a history of prior small bowel resection and stricture are a possible causes of intestinal obstruction by the passed stone via widened orifice of the sphincter.[48] Unlike EST, EPBD can preserve the sphincter of Oddi and thus decrease the risk of gallstone ileus. However, there is the possibility of small bowel obstruction by the stones extracted during the ERCP. Thus, it is recommended that large stones be removed after pulverization by mechanical lithotripsy.

5. Long-term follow-up results (Table 3)

Little is known about long-term complications of EPBD. A Japanese study with a mean overall follow-up duration of 9.3 years (7.0-12.1 years) demonstrated that 22 patients (12.1%) of 182 experienced 33 biliary complications during the follow-up period; stone recurrences in 13 patients (7.1%), stone migration from the gallbladder in 5 patients (2.7%), acute cholangitis in 10 patients (5.5%), acute cholecystitis in 4 patients (2.2%), and fatal gallstone pancreatitis in one patient (0.5%).[49] Approximately 85% of recurring bile duct stones occurred within 3 years after EPBD. All recurring stones were bilirubinate, and the majority of patients (92.3%) with stone recurrence did not have pneumobilia. Previous cholecystectomy (OR, 4.813; 95% CI, 1.237-18.726), dilated bile duct of more than 15 mm in width (OR, 4.433; 95% CI, 1.084-18.117) and no confirmation of clean duct using IDUS (OR, 11.197; 95% CI, 2.170-57.771) were significant risk factors for stone recurrence according to multivariate analysis. Although periampullary diverticulum was noted as a risk factor in another study with mid-term follow-up period (mean 23 moths),[50] it was not significant in this long-term follow-up study. Age, sex, large stone, multiple stones, multiple endoscopic sessions and mechanical lithotripsy were not associated with stone recurrence in this study, either. Between the patients younger and older than 85 years of age, there was no significantly difference in overall complications, such as cumulative stone recurrence rate (7.1% vs 7.7%, p=0.6225), acute cholangitis (1.9% vs 2.6%, p=0.7711) and acute cholecystitis (1.1% vs 2.6%, p=0.4594) during the follow-up period (mean, 61.1 months vs 39 months).[51] Remnant GB stone was one of the factors related with biliary stone recurrence. During a mean follow-

Table 3. Long Term Follow-Up Results of EPBD

Authors (published yr)	Patients' factors		Initial procedure		Follow-up results			
	Patients no.	Stone size, mm	Mechanical lithotripsy, No. (%)	Complete ratio of stone clearance, No. (%)	Follow-up duration, mo	Bile duct stone recurrence, No. (%)	Time to recurrence	Other complications
Minami *et al*.[14] (1995)	20	-	-	20 (100)	21.5±6.2	1 (5.0)	-	No complication
Yasuda *et al*.[16] (2001)	235	12.7 (4-47)	35 (15.0)	235 (100)	36.3 (12-67)	23 (10.0)	-	Acute cholangitis 0
Natsui *et al*.[25] (2002)	70	9.2 (3-22)	29 (41.4)	65 (92.9)	30 (12-54)	3 (4.4)		Acute cholecystitis 1 (3.6%)
Ueno *et al*.[50] (2003)*	169	11.8	-	162 (95.8)	23 (12-53)	13 (13.3)	12.5 mo (6-25)	Not commented
Lin *et al*.[26] (2004)	51	0.8±0.6	1 (2.0)	48 (94.1)	16±3	3 (5.8)	22-26 wk	Not commented
Vlavianos *et al*.[59] (2003)	103	≤5 (26.0%) 6-9 (36.0%) ≥10 (38.0%)	7 (6.8)	90 (87.4)	12	2 (1.9)	-	Acute cholangitis 2 (1.9%) Acute cholecystitis 2 (1.9%) Acute pancreatitis 1 (1.0%)
Tanaka *et al*.[27] (2004)	16	10.2±3.5 (5-15)	8 (50.0)	16 (100)	61.5 (54-76)	4 (25.0)	-	Acute cholecystitis 0
Ito *et al*.[51] (2008)	74 (Age≥85)	10.3±4.7	42 (57.0)	67 (91.0)	39.1	3 (7.7)	-	Acute cholangitis 1 (2.6%) Acute cholecystitis 1 (2.6%)
	332 (Age<85)	7.3±4.3	87 (26.0)	317 (95.0)	61.1	19 (7.1)	-	Acute cholangitis 5 (1.9%) Acute cholecystitis 3 (1.1%)
Ohashi *et al*.[49] (2009)†	212	10.6±5.4 (2-30)	95 (52.2)	204 (96.2)	9.3±2.4 yr (0.2-12.1)	13 (7.1)	1.7±1.7 yr (0.4-6.3)	Acute cholangitis 10 (5.5%) Acute cholecystitis 4 (2.2%) Acute pancreatitis 1 (0.5%) Mortality 1 (0.5%)‡
Kojima *et al*.[61] (2010)	453	7.7±3.5	144 (31.7)	448 (99.0)	2,214 day (336-4,442)	31 (6.8)	-	Not commented

The size of the balloon used in the endoscopic papillary balloon dilation (EPBD) procedures was approximately 8 mm, except in studies performed by Lin *et al*. (8 to 12 mm) and Vlavianos *et al*. (10 mm).
All of the patients were followed up, except in the studies of Natsui *et al*. (68, 97.1%), Ueno *et al*. (98, 58%), and Ohashi *et al*. (182, 89.2%).
Prognostic factors were determined by multivariate analysis.
*Bile duct diameter>20 mm (relative risk 6.83) and diverticulum (relative risk 6.88); †Previous cholecystectomy (odds ratio 4.8), bile duct diameter >15 mm (odds ratio 4.4) and confirmation using IDUS (odds ratio 11.2); ‡Mortality was related to gallstone pancreatitis.

up of 2,214 days, recurrence was observed more frequently in the group with GB stones.

There were several comparative studies of mid-term and long-term complications between the EPBD and EST groups. During a mean follow-up of 16 months, common bile duct stones recurred at a similar rate in both groups (5.8% at 22-26 weeks vs 7.5% at 12-48 weeks).[26] Another study compared early, mid-term and late complications of the procedure. Within 1 year of follow-up, bile duct stones recurred more frequently in the EPBD group (25.0%) than in the EST group (6.3%). On the contrary, if the follow-up period was longer than one year, stone recurrences were more common in EST group (26.7%) than the EPBD group (6.3%). A larger post-EST papillary opening facilitated spontaneous passage of small biliary duct stones. However, other factors may contribute to stone recurrence in long-term follow-up after EST, for example repeated reflux of intestinal juice to the bile duct from the duodenum. Preservation of sphincter function might prevent the stone recurrence beyond the early post procedure period.[27] After one year, SO function was not restored in the EST group, while it was signifi-

cantly recovered in the EPBD group.[16] The preservation of SO function prevents the later biliary complications. When follow-ups were done for about 3 years in the EPBD and EST groups, pneumobilia appeared at a significantly higher rate in the EST group (40.0%) than in the EPBD group (8.9%) (p<0.01). Similarly, cholecystitis was observed significantly more often in the EST group (18.8%) than in the EPBD group (4.7%) (p<0.05). Significant difference was found between the two groups with the regard to the cumulative incidence of biliary complications (p<0.05).

EPLBD

Because EPBD showed limited success rate in cases of large bile duct stones, EPLBD was attempted in 2003 by Ersoz *et al*.[40] Prior to balloon dilation of the sphincter, a small sphincterotomy incision was made from the orifice of the papilla proximally to the transverse fold. A large-diameter balloon catheter (12-20 mm) was introduced into the bile duct and gradually inflated with diluted contrast medium until the waist of balloon was disappeared, and maintained in position for a dozens of seconds (Fig. 2).

EPLBD enlarged the biliary orifice enough to facilitate removal of multiple and larger stones, resulting in a decreased use of mechanical lithotripsy and increased rate of stone removal. According to reports on the efficacy of EPLBD with EST, the complete rates of bile duct stone at first and final session were 72-100% and 95-100%, respectively (Table 4).[31,40,52-58]

Even though the stone is large, the less mechanical lithotripsy was needed with large diameter balloon plus sphincterotomy. The largest stone in the studies was up to 30 mm in diameter.[52,56] When EPLBD with a 13 mm sized balloon was used to remove the 10-30 mm sized stones, the overall success rate was 95% as usual, but mechanical lithotripsy was required in 27.0% of the cases.[52] On the other hand, when larger balloons of up to 15 mm in size were used for the removal of 6-30 mm sized stones, the overall success rate was 95% and the mechanical lithotripsy was required in only 4.5% of the cases.[56]

The efficacy of stone removal in EPLBD plus EST as compared with that of EST alone was similar. The initial success rate of EPLBD plus EST was higher than that of EST (96.2% vs 85.4%), which showed marginal statistical significance (p=0.057). Stone fragmenting by mechanical lithotripsy disturbed complete clearance and prolonged the procedure time. Because combining of EPLBD and EST reduces the need for mechanical lithotripsy (5.7% vs 25.0%, p<0.01), it effectively reduces the total procedure time (31.6±8.8 seconds vs 40.2±16.3 seconds, p<0.05) and radiation exposure (13.1±6.6 seconds vs 21.9±14.7 seconds. p<0.05).[57] The complete duct clearances in cases of stones larger than 15 mm were not significantly different between EPLBD plus EST and EST alone (94.4% vs 96.7%, p=0.569) (Table 5).[31] Mechanical lithotripsy or repetitive procedure were in fact less

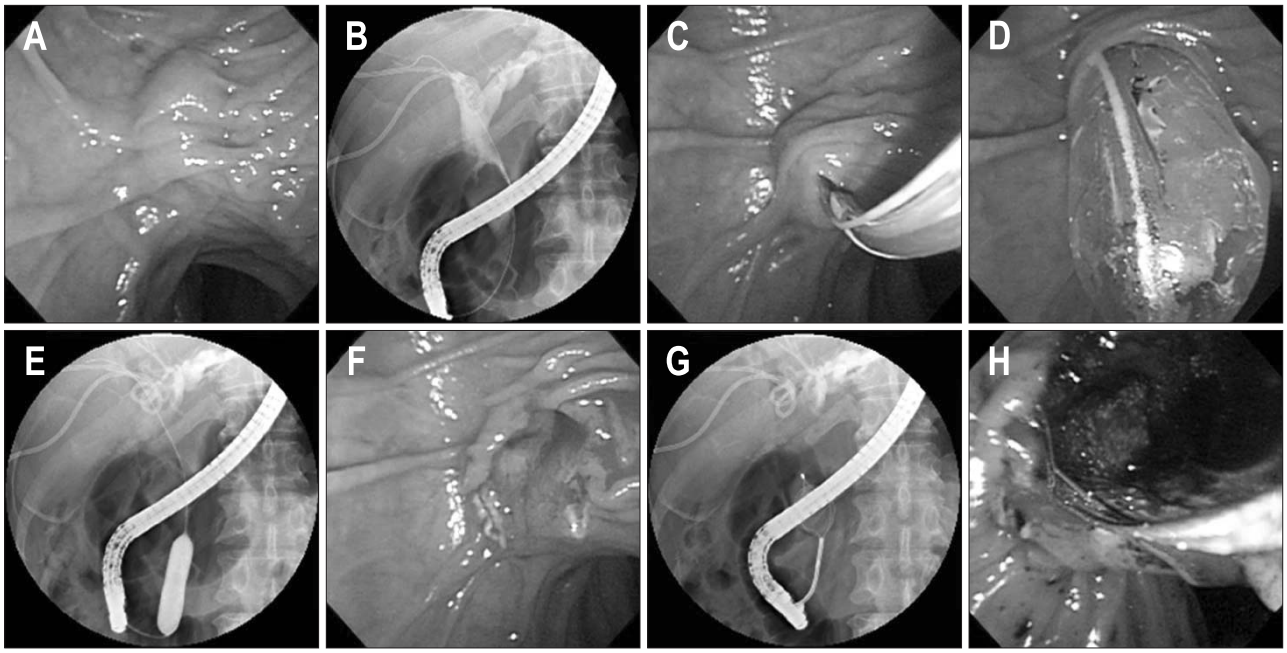

Fig. 2. Endoscopic papillary large balloon dilation (EPLBD) with limited sphincterotomy. (A) Duodenoscopic finding shows an ampulla of Vater. (B) ERCP shows a large stone in the common bile duct and percutaneous transhepatic biliary drainages placed in the right hepatic lobe. (C) A pull-type sphincterotome is inserted into the bile duct along the guidewire. The biliary sphincter is incised by electrocautery with the bowed cutting wire. (D, E) The 15 mm sized large balloon is gradually inflated with diluted contrast material; inflation is maintained for 30 seconds. (F) Duodenoscopic finding after EPLBD shows a well-visualized common bile duct with a large, dilated opening of the sphincter of choledochus. (G) ERCP shows a large stone grasped by a mechanical lithotripter. (H) Duodenoscopic finding shows stones removed from the common bile duct by a Dormia basket.

Table 4. Comparisons between EPLBD with EST (Group A) and EST Alone (Group B) for Removal of Choledocholithiasis

Authors (published yr)	Method		Patients' factors					Results			Complications
	Group	Balloon size, mm	Age, yr	Sex, M/F	Periampullary diverticulum, No. (%)	Stone no.	Stone size, mm	Mechanical lithotripsy, No. (%)	Complete ratio at first session, No. (%)	Complete ratio at the end of session, No. (%)	
Heo *et al*.[31] (2007)	A (n=100)	12-20	64.4±12.8	48/52	49 (49.0)	2.7±2.7	16±0.7	8 (8.0)	83 (83.0)	97 (97.0)	Pancreatitis 4 (4.0%) Cholecystitis 1 (1.0%) Bleeding 0 Perforation 0
	B (n=100)	-	62.8±15.7	50/50	45 (45.0)	2.2±1.9	15±0.7	9 (9.0)	87 (87.0)	98 (98.0)	Pancreatitis 4 (4.0%) Bleeding 2 (2.0%) Cholecystitis 1(1.0%) Perforation 0
Itoi *et al*.[57] (2009)	A (n=53)	15, 18, 20	75.3±12.8	20/33	25 (47.2)	3.2±3.1	14.8±3.5	3 (5.7)*	51 (96.2)	53 (100)	Pancreatitis 1 (1.9%) Cholangitis 1 (1.9%) Bleeding 0 Perforation 0
	B (n=48)	-	72.6±14.6	28/30	28 (58.3)	3.0±2.8	15.3±3.2	12 (25.0)*	41 (85.4)	47 (98.0)	Pancreatitis 2 (4.1%) Cholangitis 1 (2.1%) Bleeding 0 Perforation 0
Kim *et al*.[62] (2009)	A (n=27)	15, 16.5, 18	70.3±8.7	10/15	9 (33.3)	2.2±1.3	20.8±4.1	9 (33.3)	23 (85.0)	27 (100)	Bleeding 4 (15.0%) Pancreatitis 0 Cholangitis 0 Perforation 0
	B (n=28)	-	69.8±9.2	11/14	10 (35.7)	2.3±1.2	21.3±5.2	9 (32.1)	23 (86.0)	28 (100)	Bleeding 2 (7.0%) Pancreatitis 0 Cholangitis 0 Perforaiton 0

EPLBD, endoscopic papillary large balloon dilatation; EST, endoscopic sphincterotomy.
*p<0.01.

necessary in EPLBD plus EST. EPLBD may decrease the risks of EST and clear away larger stones in cases with difficult anatomies.

Theoretically, it is feared that large size balloon dilation could cause perforation or fatal pancreatitis, however there is only one report of cystic duct perforation[52] and none of fatal pancreatitis. On the other hands, in patients with coagulopathy who have a great risk of bleeding after EST, compression by ballooning seems to be effective for hemostasis. There are some concerns that the sphincter of Oddi could be destroyed by large sized-balloon. For lack of long-term results, we have little information of stone recurrence or cholangitis after EPLBD.

EPLBD plus EST be applied to anatomically difficult cases without critical complications but should also be confirmed by long-term follow-up studies.

CONCLUSIONS

EPBD and EPLBD seem to be safe and effective for the treatment of bile duct stones although mechanical lithotripsy is more frequently needed than in EST. Due to the preservation of SO function, EPBD seems to present less at risk of long term complications, such as stone recurrence, cholangitis and cholecystitis than EST. Although concerns were presented about post-procedure pancreatitis, recent reports have demonstrated that EPBD can be successfully and safely used for removal of small size and small unmber of stones. In patients with a higher risk of bleeding or an abnormal anatomy (periampullary diverticulum, Billrothe II gastrojejunostomy and prior EST status), EPBD is safer than EST. The most important ways to avoid severe complications are proper balloon size according to bile duct width and a wake-up not to excessively increase balloon pressure. When there are high risk factors of post ERCP panceatitis (young patients, previuos history of pancreatitis, and so on), balloon size should be as small as possible and adjuvant prophylaxis (pancreatic duct stent, gabexate mesylate, and so on) could be considered. In case of difficult cannulation, impractical cannulation should be avoided and minimal EST before balloon dilation is recommended. EPLBD could be useful adjuvant in patients with very large bile duct stones. We summarize the indications, methods, and complications of EPBD and EPLBD in Table 5. In the near future, making a guide-line for endoscopic

Table 5. Summary of EPBD and EPLBD

1. Methods	
Balloon size, mm	8-10* 10-20†
Pressure, atm	1-12
Inflation time, sec	30-180* 15-60†
2. Ideal indications	
Coagulopathy	
Periampullary diverticulum	
Billroth II gastrojejunostomy	
Prior EST status	
3. Immediate complications (n=1,457)‡	
Pancreatitis	5.1%
Biliary infection	1.9%
Bleeding	2.0%
Perforation	0.2%
Mortality	0.2%
4. Long term follow-up results (n=1,645)§	
Stone recurrence	6.7%
Biliary infection	1.7%

Biliary infection included cholangitis and cholecystitis.
EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilatation; EST, endoscopic sphincterotomy.
*EPBD; †EPLBD; ‡These results were calculated from total 23 articles (13 for EPBD and 10 for EPLBD);[15,16,23-29,31,35,37, 40,46,52-59,62] §These results were calculated from total 8 articles.[16,26,27,49-51,59,61]

management of bile duct stones according to the individual patient's characteristics (e.g., age, coagulopathy, previous history of EST, pancreatitis and gastric operation) and bile duct stone characteristics (e.g., size, number) will be helpful to gastroenterologist.

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