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Endoscopic papillary large balloon dilation with minor sphincterotomy for periampullary diverticular papilla

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ABSTRACT

Background: to observe the outcome of endoscopic papillary large balloon dilation (EPLBD) with minor sphincterotomy (mEST) for periampullary diverticular papilla

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related to stone removal.

Methods: patients with confirmed periampullary diverticulum (PAD) during stone removal from May 2016 to April 2018 were reviewed retrospectively. The Chi-squared test with Yates correction or Fisher's exact test was used for the analysis of categorical data and a normality test was applied for continuous data.

Results: a total of 154 consecutive patients (89 males and 65 females, aged 51-87 years) with confirmed PAD during stone removal were included in the study. Cases were divided into the conventional endoscopic sphincterotomy (EST) group (n = 79) and the mEST plus EPLBD group (n = 75). The number of patients with an initial treatment success was greater in the EPLBD+mEST group compared with the EST group (96% *vs* 86.1%, p = 0.03) and the procedure time for EPLBD+mEST was shorter than that for EST alone (46.1 ± 13.7 min *vs* 53.3 ± 11.6 min, p = 0.01). The rate of complications in the EPLBD+mEST group was lower than in the EST group (17.3% *vs* 32.9%, p = 0.04). When PAD was > 15 mm, the initial success rate was higher (92.6% *vs* 73.9%, p = 0.04) and the rate of overall complications was lower (14.8% *vs* 41.7%, p = 0.03) in the EPLBD+mEST group than those in the EST group. However, this was similar when PAD was < 15 mm.

Conclusion: EPLBD+mEST might be safer and more effective than conventional EST alone for stone removal in the presence of PAD.

Key words: Periampullary diverticulum. Endoscopic papillary balloon dilation. Pancreatitis. Sphincterotomy.

INTRODUCTION

Periampullary diverticulum (PAD) is the extraluminal outpouching of the duodenal mucosa and muscularis mucosae adjacent to or containing the ampulla of Vater (1,2). PAD is rare in patients aged < 40 years. Previous studies (3-6) have reported a prevalence of PAD between 5% and 36% in different populations. However, this increased with age (7-10) and the overall prevalence among the elderly was up to 65% (11,12). PAD is a concern during endoscopic retrograde cholangiopancreatography (ERCP) due to its association with an increased incidence

of pancreaticobiliary disease and its adverse influence on ERCP procedures. Selective biliary cannulation with a side-viewing endoscope is sometimes difficult in patients with PAD due to the uncertain anatomy and deformation of the duodenal papilla. The reported success rate of cannulation in patients with PAD varies from 61% to 95.4%. This is significantly lower than that observed in patients without PAD (13). As a result, new procedures such as cap-assisted cannulation (14) and endoclip-assisted cannulation (15) have been adopted to increase the success rate of selective biliary cannulation. However, the efficacy and safety of regularly used methods to open the duodenal papillary orifice, including standard endoscopic sphincterotomy (EST) and minor EST following endoscopic papillary large balloon dilation (EPLBD+mEST), are rarely reported in patients with PAD. In fact, the potential risk of complications is increased in patients with PAD, due to the thin mucosa and the lack of the sphincter muscle present in the ampullary area (15-17). However, few studies to date have focused on the influence of PAD on different methods for opening the duodenal papillary orifice. Thus, this retrospective comparative study was performed to determine which method is more efficient and safer to open the duodenal papillary orifice in patients with PAD.

MATERIALS AND METHODS

Patients

The profiles of patients who underwent therapeutic ERCP for common bile stone (CBD) removal with confirmed PAD during the procedure were reviewed. Cases were included in the study from three centers (Changshu Affiliated Hospital of Soochow University, The First Affiliated Hospital of Soochow University and Ao Yang Hospital of Zhang Jia Gang) between May 2016 and April 2018. The exclusion criteria were: a) pre-existing acute pancreatitis; 2) previous ERCP-related procedures; 3) the presence of intrahepatic duct stones, distal bile duct strictures or malignant biliary obstruction; and 4) coagulopathy, platelet count < 50,000/ml or anticoagulation therapy within the previous week.

Endoscopic procedures

All ERCP-related procedures were performed according to the standardized protocol by three endoscopists (JH Qian, CF Xu and ZX Sun), each with over 15 years of ERCP experience. The procedure was performed using a side-viewing duodenoscope (TJF-260, Olympus Corp., Tokyo, Japan) with a large accessory channel. Local anesthesia of the pharynx was performed using 10% xylocaine and an intramuscular injection of 40 mg hyoscine butylbromide and 50-100 mg meperidine were administered as premedication. PAD was defined as the presence of a diverticulum within a 2-3 cm radius of the papilla. After selective cannulation, EST alone or minor EST+EPLBD were performed according to preferences and habits of endoscopists. Stones were then extracted from the bile duct using conventional methods, such as a Dormia basket catheter, a balloon extractor or a mechanical lithotripter (BML-4Q, Olympus® Corp., Tokyo, Japan) when required. Complete stone removal was confirmed by cholangiography.

EST was performed according to the conventional method with a pull-type sphinctertome, accomplished by extending the incision up to the major horizontal fold crossing the intramural portion of the bile duct. The extent of sphincterotomy was dependent on the size of the stones and the distal bile duct. The mEST was performed from the orifice of the papilla proximally, but did not extend beyond the horizontal fold or the transverse fold of the papilla. EPLBD was performed following mEST using a dilating balloon (5.5 cm in length, 12-20 mm, Boston Scientific, Corp., MA, USA). The diameters of the balloons were set at 12-20 mm, based on the size of the stones and the distal bile duct.

Post-operative management

An endoscopic nasobiliary drainage (ENBD) catheter (7.5F, Boston Scientific Corp., MA, USA) was routinely inserted after endoscopic clearance of the CBD stones. This was withdrawn at least 48 hours after ERCP if there were no remnant stones on cholangiography and symptoms and abnormal laboratory values improved (defined as an initial success). If not, a second session of ERCP was performed to retrieve the remnant stones. All enrolled patients were hospitalized and routinely received antibiotics following ERCP.

Classification of periampullary diverticulum

PAD was classified as type I or II according to the location of the papilla and diverticulum (18): type I or extradiverticular papilla: the papilla was at the rim or within 2 cm from the edge of the diverticulum; and type II, or intradiverticular papilla: the papilla was inside or between two adjacent diverticula.

The size of PAD was classified as small or large when the diameter of PAD was < 15 mm or ≥ 15 mm, respectively. A 15-mm extraction balloon was used during ERCP to estimate PAD size. If there was more than one PAD present, the sum of the diameters was chosen as the representative size.

Definition of post-endoscopic retrograde cholangiopancreatography complications

Post-ERCP pancreatitis (PEP) was defined as abdominal pain with at least a three-fold elevation in serum amylase more than 24 hours after the procedure. Mild PEP required treatment for 2-3 days, moderate PEP required treatment for 4-10 days and severe PEP required more than ten days hospitalization (19,20). Post-ERCP cholangitis (PEC) was defined as a fever higher than 38 °C that lasted for more than 48 h due to biliary causes (19). Hemorrhage was defined as mild when there was a decrease in hemoglobin level, moderate when transfusion was required (< 4 units) and severe when more than five units of blood were needed or when an intervention was required (19).

Statistical analysis

Statistical analyses were performed on a per-protocol basis using the SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). The X^2 test with Yates correction or Fisher's exact test were used for the analysis of categorical data. A normality test was applied for continuous data, which was then analyzed with the Student's t test or Mann-Whitney U-test where appropriate. Patient characteristics are expressed as the mean ± standard deviation or as percentages. All statistical tests were two-tailed and the threshold for statistical significance was set at $p < 0.05$.

RESULTS

A total of 1,579 patients received therapeutic ERCP at three centers between May 2016 and April 2018. Of these, 167 (10.6%) patients were diagnosed with PAD. Thirteen patients with PAD did not meet the inclusion criteria (seven cases had concomitant malignant diseases and six cases did not have choledocholithiasis during ERCP) and were excluded. The remaining 154 cases (89 males and 65 females, age range 51-87 years) received either standard EST (n = 79) or EPLBD+mEST (n = 75). The two groups did not differ with regard to baseline characteristics and laboratory findings. Furthermore, the maximum diameter of the CBD, stone size, and the type and size of PAD were similar in both groups (Table 1). There was no difference between the two groups in terms of the duration of cannulation (19.1 ± 11.7 min *vs* 18.5 ± 10.7 min, p = 0.74). Overall, three (1.9%) patients underwent pre-cut papillotomy due to a difficult bile duct cannulation, one in the EST group and two in the EPLBD+mEST group. There were no statistically significant differences.

The data on endoscopic procedures and treatment are shown in table 2. CBD stone clearance was successfully performed in 153 (99.4%) patients with an initial success in 140 (90.9%) patients. The overall success in the two groups was similar and more patients had an initial success in the EPLBD+mEST group than in the EST group (96% *vs* 86.1%, p = 0.03). The procedure time in the EPLBD+mEST group was shorter than that in the EST group (46.1 ± 13.7 min *vs* 53.3 ± 11.6 min, p = 0.01). The use of mechanical lithotripsy, duration of ENBD placement and hospital stay following ERCP in the two groups were similar.

The rate of complications in the EPLBD+mEST group was lower than in the EST group (10.7% *vs* 22.8%, p = 0.04). Seventeen (11%) patients developed PEP, most were mild to moderate in severity and were resolved with conservative treatment, except for one patient in the EST group with severe pancreatitis (with a perforation) who subsequently died. No significant difference in PEP between the two treatments was observed (EST and EPLBD+mEST, 13.9% *vs* 8%, p > 0.05), regardless of the severity of PEP. In addition, no significant differences with respect to the rates of PEC were found between the two treatment groups (EST and EPLBD+mEST, 11.4% *vs* 6.7%, p > 0.05). Six (3.9%) patients developed hemorrhage, one (1.3%) in the EPLBD+mEST

group and five (6.3%) in the EST group (p > 0.05); all were mild and quickly controlled. One case in each group developed a perforation (1.3% *vs* 1.3%, p = 1.00). The patients were divided into two subgroups according to the size of PAD < 15 mm or ≥ 15 mm. The data on endoscopic procedures and ERCP-related complications are shown in table 3. There was no difference in the overall success rate of stone removal between the EPLBD+mEST and EST groups, irrespective of the size of PAD. The initial success rate in the EPLBD+mEST group was higher than that in the EST group (92.6% *vs* 73.9%, p = 0.04) when PAD was > 15 mm. However, this difference was not found when PAD was < 15 mm. The procedure time for EPLBD+mEST was shorter than that for EST alone, whether the diameter of PAD was < 15 mm (45.9 ± 11.7 min *vs* 52.3 ± 11.9 min, p = 0.01) or > 15 mm (48.9 ± 14.7 min *vs* 54.7 ± 13.9 min, p = 0.04). The rate of overall complications was lower in the EPLBD+mEST group than in the EST group when PAD was > 15 mm (14.8% *vs* 41.7%, p = 0.03), but was similar when PAD was < 15 mm.

DISCUSSION

The formation of PAD is associated with congenital and acquired factors. Congenital PAD is the result of a defect during the development of the embryonic foregut and midgut at the fusion site. The developmental defect leads to a lack of intestinal smooth muscle or the formation of collapsible muscular diverticula (21). The acquired risk factors include advanced age, progressive weakening of intestinal smooth muscle and increased intraduodenal pressure (22). The overall incidence of PAD was 10.6% in this study, which is consistent with previous reports (3-10). All patients included in this study were > 50 years old. PAD is usually asymptomatic. However, it is thought to be related to acute pancreatitis, cholelithiasis, dilated bile duct and primary or recurrent CBD stones (3,6,7,9). In addition, selective biliary cannulation can be difficult, time consuming and challenging for most endoscopy specialists in PAD cases (23). Especially the intradiverticular papilla type, with an unusual papillary anatomy and an uncertain biliary direction. These factors may lead to pancreatitis due to the unnecessary injection of contrast medium or manipulation of the pancreatic duct (24). Thus, a number of specialized techniques have been

used for successful biliary cannulation (14,15,25). However, there are several studies (4,8,18) that do not regard PAD as a barrier to a successful cannulation. Nevertheless, this was not the topic of the current study and the view that PAD could increase the incidence of ERCP-related complications is generally accepted. This study was performed to evaluate the efficacy and safety of different methods for opening the duodenal papillary orifice in patients with PAD.

Although the duration of cannulation was similar in both groups ($p = 0.7407$), the current results demonstrated that the procedure time in the EPLBD+mEST group was shorter than that in the EST group. Independently of whether the diameter of PAD was < 15 mm or > 15 mm. The initial success of stone clearance was 90.9% in the EPLBD+mEST group, which was significantly higher than that in the EST group ($p < 0.05$). However, this difference was not found in patients with small PAD ($p > 0.05$). No studies have evaluated the procedure time and initial success rate of stone clearance in patients with PAD and most studies have focused on increasing the success rate of cannulation (8,14,15,23). We hypothesized that large balloon dilation together with minor sphincterotomy could facilitate CBD stone removal and sig nificantly shorten the ERCP procedure time in patients with PAD. Findings in a previous study focused on biliary sphincterotomy dilation for the extraction of difficult common bile duct stones (26). In addition, it could also increase the initial success rate of stone clearance, especially in patients with a large PAD.

Mechanical lithotripsy has proven to be a challenging technique, with related adverse events such as basket impaction and bile duct injury (27,28). It was reported that EPLBD could reduce the use of mechanical lithotripsy for the removal of large or difficult bile duct stones (29). However, this was not confirmed in the current study. We speculated that the reason for this was that the size of most stones was less than 15 mm, which were successfully extracted using a Dormia basket catheter or a balloon extractor.

Two previous studies (4,8) evaluated the safety of stone removal by EPLBD+mEST and standard EST in patients with PAD. However, the conclusions in these studies were contradictory. Although there were no differences detected in terms of PEP, PEC, hemorrhage or perforation, the current results supported one of the earlier

studies (8). Specifically, that EPLBD+mEST was safer than EST for removing bile duct stones in patients with PAD, due to a significantly lower overall complication rate ($p = 0.0448$). Furthermore, the results showed that the statistical differences in overall complications mainly occurred in patients with large PAD ($p = 0.0320$) and not in patients with small PAD ($p > 0.05$). In general, balloon dilation induces pancreatitis more frequently than EST. In this study, there was no difference in the post-ERCP pancreatitis ratio between the two groups. Thus, we speculated that this was due to the fact that all patients included received prophylactic rectal indomethacin and ENBD placement routinely after stone clearance. These methods have confirmed the ability to reduce the incidence and severity of PEP (30-32).

One patient in each group developed a perforation. The patient in the EST group was an elderly woman with an extradiverticular papilla. The perforation was found after the procedure due to a huge hematoma under the liver and severe PEP detected by computed tomography scanning, along with abdominal pain and fever. The patient died due to secondary multiple organ failure. The patient in the EPLBD+mEST group was also an elderly woman with an intradiverticular papilla and cannulation was difficult as it took a long time to successfully insert the guidewire into the bile duct. However, perforation occurred during stone extraction and was confirmed by computed tomography scanning. This patient was managed conservatively with oxygen supplementation, nasogastric tubing, parenteral nutrition and broad-spectrum antibiotics, and eventually recovered. The influence of different types of PAD on post-ERCP complications has rarely been reported. Kim et al. (24) reported that the incidence of PEP in patients with intradiverticular papilla was higher than that in the extradiverticular papilla group (14.3% *vs* 5.3%, $p < 0.05$). However, no differences were found in another recent study (4). This study reported a similar incidence of post-ERCP complications in different types of PAD, with the exception of a slightly higher rate of PEP in patients with intradiverticular papilla. As intradiverticular papilla is very rare and only seven (4.5%) patients with intradiverticular papilla were included in this study, we did not analyze the impact of different treatments on different types of PAD. Thus, this was a limitation of the current study. Additional limitations included the retrospective nature of the study,

which could result in a potential bias in the selection of patients and procedures. A prospective randomized study is needed in the future to confirm the results.

In conclusion, EPLBD combined with mEST may be safer and more effective than EST alone for CBD stone removal in patients with PAD. This technique may increase the initial success rate of CBD stone clearance and play a role in reducing the development of early complications, particularly in patients with large PAD.

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Table 1. Comparison of baseline characteristics and laboratory findings between the two groups

Variable	EST (n = 79)	EPLBD+mEST (n = 75)	*p*
Age, y	62.1 ± 13.5	61.7 ± 12.7	NS
Gender, male/female	45/34	47/28	NS
Cholecystolithiasis, n (%)	19 (24.1%)	22 (29.3%)	NS
Cirrhosis, n (%)	6 (7.5%)	5 (6.7%)	NS
History of cholecystectomy, n (%)	7 (8.9%)	9 (12%)	NS
Billroth II gastrectomy, n (%)	1 (1.3%)	1 (1.3%)	NS
Size of PAD, mm	13.3 ± 3.5	12.3 ± 3.7	NS
Type of PAD (I/II)	76/3	71/4	NS

Amylase, U/l	91.1 ± 24.3	81.1 ± 21.9	NS
Total bilirubin, mg/dl	7.3 ± 2.6	7.9 ± 2.1	NS
Alanine transaminase, IU/l	119.3 ± 37.2	127.8 ± 27.1	NS
Prothrombin time, s	10.7 ± 2.3	10.2 ± 2.1	NS
Platelet count, ×106/l	138.1 ± 31.2	147.2 ± 31.3	NS
Maximum CBD diameter, mm	14.1 ± 4.7	14.5 ± 3.6	NS
Maximum stone diameter, mm	10.1 ± 4.7	10.4 ± 4.1	NS
Number of CBD stones	2.3 ± 1.9	2.9 ± 1.1	NS

NS: not significant.

Table 2. Comparison of endoscopic procedures and treatment between the two groups

	Overall (n = 154)	EST (n = 79)	EPLBD+mEST (n = 75)	p
Overall success, n (%)	153 (99.4)	79 (100)	74 (98.7)	NS
Initial success, n (%)	140 (90.9)	68 (86.1)	72 (96)	0.03
Balloon diameter, median (range), mm	12.9 (12-16)	13.0 (12-16)	12.8 (12-16)	NS
Procedure time, min	49.5 ± 12.2	53.3 ± 11.6	46.1 ± 13.7	0.01
Mechanical lithotripsy	5 (3.2)	3 (3.8)	2 (2.7)	NS
Duration of ENBD placement, hours	63.4 ± 11.1	64.5 ± 12.4	62.1 ± 11.3	NS
Duration of hospital stay, days	6.2 ± 2.2	6.3 ± 2.0	5.9 ± 2.3	NS

NS: not significant.

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Table 3. Influence of different PAD size on treatment outcome

Variable	PAD < 15 mm			PAD ≥ 15 mm		
	EST (n = 55)	EPLBD+mEST (n = 48)	p	EST (n = 24)	EPLBD+mEST (n = 27)	*p*
Overall success, n (%)	55 (100)	48 (100)	NS	24 (100)	26 (96.3)	NS
Initial success, n (%)	51 (92.7)	47 (97.9)	NS	17 (73.9)	25 (92.6)	0.04
Mechanical lithotripsy	0	1 (2.1)	NS	3 (1.3)	1 (3.7)	NS
Procedure time, min	52.3 ± 11.9	45.9 ± 11.7	0.0072	54.7 ± 13.9	48.9 ± 14.7	0.04
Duration of ENBD placement, hours	63.1 ± 11.4	61.1 ± 13.3	NS	64.9 ± 12.7	62.9 ± 14.1	NS
Duration of hospital stay, days	6.1 ± 2.3	5.8 ± 2.7	NS	6.5 ± 1.7	6.2 ± 2.1	NS
PEP (%)	3 (5.5)	3 (6.3)	NS	8 (33.3)	3 (11.1)	NS
PEC (%)	4 (7.3)	2 (4.2)	NS	5 (20.8)	3 (11.1)	NS
Hemorrhage (%)	2 (3.6)	0	NS	3 (12.5)	1 (3.7)	NS
Perforation (%)	0	0	NS	1 (4.2)	1 (3.7)	NS
Overall complications (%)*	8 (14.5)	4 (8.3)	NS	10 (41.7)	4 (14.8)	0.03

*A patient may develop more than one type of complication. NS: non-significant.