Endoscopic papillary balloon dilation can be safely performed in patients with dual antiplatelet therapy: A pilot study

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Abstract

Endoscopic papillary balloon dilation (EPBD)—a low-risk procedure for bleeding—has been suggested as an alternative to endoscopic sphincterotomy (EST) for papillary dilatation in patients undergoing choledocholithotomy and at a high risk of bleeding. Several guidelines recommend dual antiplatelet therapy (DAPT) be reduced to single antiplatelet therapy (SAPT) when EST is performed. However, there is no evidence that EPBD increases the risk of bleeding in patients receiving DAPT. Thus, we aimed to address this problem. We included 31 patients who underwent EPBD for CBD stones and received DAPT or SAPT prior to EPBD (9 in the DAPT group and 22 in the SAPT group) treated at our hospital from May 2014 to August 2022. The DAPT group included patients who underwent EPBD without antiplatelet therapy withdrawal or with a shorter withdrawal period than those recommended by the guidelines. In the DAPT group, one of the two antiplatelet agents used was thienopyridine. No bleeding was observed after EPBD in this study. We did not find any significant between-group differences in the change in hemoglobin levels and post-ERCP pancreatitis. Thus, we propose that EPBD does not increase the bleeding risk in patients with DAPT.

Background

It is well documented that aspirin and antiplatelet agents (APAs) increase the risk of gastrointestinal bleeding\[1, 2\]. APAs, such as thienopyridines, bind to the P2Y12 component of the ADP receptor on platelets and irreversibly inhibit platelet function for 7–10 days. Thienopyridines have been reported to increase bleeding rates in endoscopic procedures with a high risk of bleeding, especially endoscopic submucosal dissection and endoscopic mucosal resection\[3\]. Therefore, several professional societies suggest performing high-risk elective endoscopic procedures, such as endoscopic sphincterotomy (EST), 5–7 days after thienopyridine drug cessation, while aspirin may be continued\[4–6\]. The European Society of Gastrointestinal Endoscopy (ESGE), American Society of Gastrointestinal Endoscopy (ASGE), and Japan Gastroenterological Endoscopy Society (JGES) guidelines recommend that dual antiplatelet therapy (DAPT) be reduced to single antiplatelet therapy (SAPT) when EST is performed (5–7 days of thienopyridine drug cessation, while aspirin or cilostazol is continued)\[6–8\]. In this situation, there is a risk of prolonged hospitalization and thrombosis owing to the required withdrawal period\[3\]. This also exposes patients to the risk of several well-documented complications of prolonged hospitalization, including pneumonia, venous thromboembolism, and muscle loss (especially in elderly patients) \[9, 10\]. In cases of cholangitis with choledocholithiasis, the number of endoscopic retrograde cholangiopancreatography (ERCP) sessions increases because of the two-stage treatment, in which a bile duct stent is placed first, and stones are retrieved after DAPT is reduced to SAPT.

In choledocholithotomy for common bile duct (CBD) stones, endoscopic papillary balloon dilation (EPBD)—a low-bleeding risk procedure—is described in the JGES, ASGE, and ESGE guidelines as a papillary dilatation procedure in patients at high risk of bleeding and an alternative to EST \[11–13\].
A systematic review of retrospective studies analyzed EST, a high-bleeding risk procedure, and EPBD, a low-bleeding risk procedure, and noted that they may not increase bleeding in patients receiving DAPT\textsuperscript{14}. However, only a small number of EPBD with DAPT patients were included in said study, and the withdrawal duration of DAPT and breakdown of antiplatelet agents used were not described\textsuperscript{15}.

Generally, EPBD has a reported bleeding rate of less than 1\% and a lower risk of bleeding than EST, and EPBD may be performed in patients receiving DAPT with low-bleeding risk\textsuperscript{14,16,17}. However, no reports have focused on EPBD in patients receiving DAPT.

Thus, there is no evidence that EPBD increases the risk of bleeding in patients with DAPT, and the benefits of reducing it to SAPT are not clear. Therefore, we propose the hypothesis that EPBD does not increase bleeding risk in patients with DAPT, and treating these cases with EPBD without DAPT withdrawal leads to a reduction in the number of ERCPs, shorter hospital stay, and avoidance of an increased risk of embolism during the DAPT reduction period in DAPT cases.

**Methods**

The study was reviewed and approved by the Institutional Review Board of the Future Medical Research Center (IRB No. TGE02046-024). All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

**Protocol Registration**

Protocol registration
The protocol was registered in the UMIN Clinical Trials Registry (UMIN-CTR) on October 13, 2022 (UMIN-CTR; No.: UMIN000049209; URL: https://www.umin.ac.jp/ctr/index.htm).

**Study population**

This retrospective study was conducted at the Shonan Kamakura General Hospital in Japan. Study enrollment commenced in May 2014 and ended in August 2022. This study included patients who underwent EPBD for CBD stones and received DAPT or SAPT prior to EPBD. Patients receiving warfarin or other anticoagulant therapies were excluded (Fig. 1). We investigated the patient characteristics, ERCP findings, incidence of EPBD bleeding, and complications associated with EPBD.

Of the 134 patients enrolled, 103 were excluded based on the exclusion criteria. Finally, 31 patients were included in the analysis (Fig. 1).

**Endoscopic procedure**

EPBD was performed using biliary balloon dilation catheters (REN; Kaneka medics, Osaka, Japan), Hurricane (Boston Scientific Japan, Tokyo, Japan), and ZARA (Kaneka medics, Osaka, Japan) through a
side-viewing endoscope (JF-260V, TJF-290V; Olympus, Tokyo, Japan). EPBD was performed by experts who had performed >1000 ERCP procedures. After EPBD balloon insertion into the papilla, the balloon was gradually pressurized until the waist disappeared. In principle, the EPBD selected a balloon diameter of 8 mm and dilated until the waist disappeared; however, in cases with a distal bile duct diameter < 6 mm, the bile duct was dilated at low pressure regardless of the disappearance of the waist.

**Antiplatelet agents**

DAPT is recommended for reduction to SAPT in JGES, ESGE, and ASGE guidelines [6-8], with a reduction to aspirin or cilostazol alone, and with a 5- to 7-day break for thienopyridines followed by high-bleeding risk procedure. In principle, EPBD was performed as a low-risk bleeding procedure with continued DAPT, and in patients on DAPT who were not at high risk of thromboembolism due to discontinuation of APAs, EPBD was performed as a high-risk bleeding procedure with a dose reduction from DAPT to SAPT.

**Definitions**

The DAPT group included patients who underwent EPBD without antiplatelet therapy withdrawal or with a shorter withdrawal period than those recommended by the guidelines.

EPBD bleeding was defined as bleeding occurring after EPBD, which was subsequently defined as bleeding requiring red blood cell transfusion, endoscopic hemostasis, or transcatheter arterial embolization within two weeks of EPBD.

**Statistical analysis**

We compared bleeding after EPBD, hemoglobin change within one week after EPBD, and post-ERCP pancreatitis outcomes in the DAPT and SAPT groups. The primary study outcome was bleeding after the EPBD. The Mann-Whitney U test was used to compare continuous variables that were non-normally distributed, and the χ²-test or Fisher's exact test was used to compare categorical variables. Multivariate analysis was performed using a logistic regression analysis. Differences were considered statistically significant at two-tailed p-values < 0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), which is a modified version of the R commander designed to allow additional statistical functions that are frequently used in biostatistics [18].

**Results**

**Patient characteristics**

Table 1 summarizes patient characteristics. We retrospectively analyzed the data of 31 patients who received antiplatelet therapy and underwent EPBD. Of these, 9 patients (29%) received DAPT, and 22 (71%) received SAPT. There were no significant between-group differences in age, sex, complicated cholangitis, underlying disease, platelet count, PT, or PT-INR between the groups. In the present study, most of the cases were complicated by cholangitis. Table 2 shows the breakdown of antiplatelet agents;
all patients in the DAPT group received thienopyridine. Table 3 summarizes the duration of incomplete thienopyridine withdrawal in the DAPT cases; five patients did not withdraw from DAPT, while four patients withdrew incompletely.

Table 1
Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>DAPT group, n = 9</th>
<th>SAPT group, n = 22</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (IQR)</td>
<td>85 (76–90)</td>
<td>82 (70–87)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>8 (88.9)</td>
<td>11 (50.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiovascular, n (%)</td>
<td>6 (66.7)</td>
<td>13 (59.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Cerebral bleeding, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>3 (33.3)</td>
<td>10 (45.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cholangitis, n (%)</td>
<td>9 (100)</td>
<td>19 (86.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (44.4)</td>
<td>5 (22.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hemodialysis patients, n (%)</td>
<td>1 (11.1)</td>
<td>1 (4.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Liver cirrhosis, n (%)</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>PT-INR (IQR)</td>
<td>1.05 (1.03–1.16)</td>
<td>1.07 (0.98–1.15)</td>
<td>0.61</td>
</tr>
<tr>
<td>PT, % (IQR)</td>
<td>91.0 (76.9–95.7)</td>
<td>87.4 (76.5-103.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Platelet, 10^4/ul (IQR)</td>
<td>18.00 (14.6–19.3)</td>
<td>19.8 (16.0-21.5)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

We retrospectively analyzed the data of 32 patients who received antiplatelet therapy and underwent EPBD. Of these, 9 patients (28%) received DAPT and 22 (72%) received SAPT. There were no significant between-group differences in age, sex, complicated cholangitis, underlying disease, platelet count, PT, or PT-INR between the groups.

IQR, interquartile range; PT-INR, prothrombin time-international normalized ratio; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; EPBD, endoscopic papillary balloon dilation.
Table 2
Breakdown of antiplatelet agents.

<table>
<thead>
<tr>
<th></th>
<th>DAPT group, n = 9</th>
<th>SAPT group, n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Sarpogrelate hydrochloride</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ethyl icosapentate</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

All patients in the DAPT group used thienopyridine.

DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; EPBD, endoscopic papillary balloon dilation.

Table 3
Duration of incomplete thienopyridine withdrawal in DAPT cases

<table>
<thead>
<tr>
<th>Thienopyridine withdrawal in DAPT cases (days)</th>
<th>DAPT group, n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>No interruption</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Five patients did not withdraw from the DAPT, while four patients withdrew incompletely.

DAPT: dual antiplatelet therapy, EPBD: endoscopic papillary balloon dilation

**ERCP findings**

Table 4 summarizes the ERCP findings in the study population. There were no significant between-group differences in difficult endoscopic biliary cannulation, peri-ampullary diverticulum, endoscopic nasobiliary drainage, choledocholithotomy, pancreatography, plastic stents in the bile duct or pancreatic duct, self-expandable metallic stents, ERCP procedure time, CBD diameter, or CBD stone diameter.
Table 4
ERCP findings

<table>
<thead>
<tr>
<th></th>
<th>DAPT group, n = 9</th>
<th>SAPT group, n = 22</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulum, n (%)</td>
<td>3 (33.3)</td>
<td>9 (40.9)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Difficult biliary cannulation, n (%)</td>
<td>2 (22.2)</td>
<td>5 (22.7)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Cases of a guidewire inserted into the pancreatic duct, n (%)</td>
<td>2 (22.2)</td>
<td>5 (22.7)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Cases with pancreatography, n (%)</td>
<td>3 (37.5)</td>
<td>8 (36.4)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Diameter of CBD, mm (IQR)</td>
<td>10 (7.0–10.0)</td>
<td>8.5 (7.3–9.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diameter of CBD stone, mm (IQR)</td>
<td>5.0 (3.0–8.0)</td>
<td>5.0 (3.0–7.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Passed stone, n (%)</td>
<td>0 (0)</td>
<td>5 (22.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lithotripsy, n (%)</td>
<td>8 (88.9)</td>
<td>22 (100)</td>
<td>0.29</td>
</tr>
<tr>
<td>ENBD, n (%)</td>
<td>2 (22.2)</td>
<td>2 (9.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Cases in which CBD plastic stents were implanted, n (%)</td>
<td>1 (11.1)</td>
<td>1 (4.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Cases in which CBD SEMS were implanted, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Cases in which pancreatic duct plastic stents were implanted, n (%)</td>
<td>1 (11.1)</td>
<td>1 (4.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>ERCP time, min (IQR)</td>
<td>25 (20–30)</td>
<td>20 (17–25)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

There were no significant between-group differences in difficult endoscopic biliary cannulation, periampullary diverticulum, endoscopic nasobiliary drainage, choledocholithotomy, pancreatography, plastic stent in the bile duct or pancreatic duct, self-expandable metallic stent, ERCP procedure time, bile duct diameter, or bile duct stone diameter.

CBD, common bile duct; IQR, interquartile range; ENBD, endoscopic nasobiliary drainage; SEMS, self-expandable metallic stent; ERCP, endoscopic retrograde cholangiopancreatography; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; EPBD, endoscopic papillary balloon dilation.

**EST bleeding and outcomes**

Table 5 summarizes the clinical outcomes of the study. No bleeding occurred after EPBD in the 31 patients in this study. We did not find any significant between-group differences in the changes in hemoglobin (Hb) levels and post-ERCP pancreatitis (PEP). All PEP cases were mild.
### Table 5
Direct oral anticoagulant cessation period

<table>
<thead>
<tr>
<th></th>
<th>DAPT group, n = 9</th>
<th>SAPT group, n = 22</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding after EPBD, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin change within 1 week after EPBD, g/dl (IQR)</td>
<td>-1.3 (-2.1 to -1.2)</td>
<td>-1.25 (-1.7 to -0.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>PEP, n (%)</td>
<td>2 (22.2%)</td>
<td>3 (13.6%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

No bleeding occurred after EPBD in the 31 patients in this study. We did not find any significant between-group differences in the changes in hemoglobin levels and post-ERCP pancreatitis. All PEP cases were mild.

**EPBD**, endoscopic papillary balloon dilation; **IQR**, interquartile range; **PEP**, post-ERCP pancreatitis; **DAPT**, dual antiplatelet therapy; **SAPT**, single antiplatelet therapy.

### Discussion

In the JGES and ASGE guidelines, EPBD is a low-risk procedure in terms of bleeding; however, the evidence for EPBD in DAPT cases is lacking [6, 13]. Nevertheless, since EST may be safely performed in DAPT cases, EPBD, which has a lower bleeding rate than EST, may be even safer [14, 19]. Therefore, we conducted this study to propose the hypothesis that EPBD can be safely performed in patients on DAPT without APAs withdrawal.

In this study, post-EPBD bleeding was not observed in any patient. There is a question of whether DAPT cases might have more minor bleeding that would stop spontaneously, but there was also no significant difference in hemoglobin change compared with the SAPT group to suggest this.

Furthermore, thienopyridines have been reported to increase bleeding rates in endoscopic procedures with a high risk of bleeding [3]. It is noteworthy that all DAPT cases in this study included thienopyridines, but there were no bleeding complications.

For mild or moderate cholangitis due to choledocholithiasis, it is also acceptable in the Tokyo Guidelines 2018 to perform choledocholithotomy simultaneously with drainage depending on the patient’s situation [20]. However, in patients receiving DAPT, stenting is performed at the first ERCP, APAs are withdrawn, and choledocholithotomy is performed at the second ERCP; if EPBD can be performed without APA withdrawal, the number of ERCPs, length of hospital stay, and risk of thrombosis owing to the required withdrawal period can be reduced [3].

Moreover, EPBD has been suspected to increase the risk of PEP [21], but several studies have disproven this [22, 23]; furthermore, there are studies based on race that show no increase in Asian populations [19]. In addition, the efficacy of prophylactic drugs for PEP, such as nonsteroidal anti-inflammatory drugs.
(NSAIDs), has been demonstrated in recent years\(^{[24]}\), and the efficacy of the combination of NSAIDs and nitrates has also been studied\(^{[25]}\). Therefore, it has been possible to reduce the incidence of PEP.

This study had a few limitations. First, it was a retrospective, single-center study with a small number of cases. Therefore, this study only suggests a hypothesis, and we would like to verify the risk of bleeding due to EPBD being performed on patients on DAPT in future prospective multicenter studies. Second, we considered aligning background factors by propensity score matching, but it was difficult to do so homogeneously; therefore, we conducted an analysis of all cases (Supplement 1).

**Conclusion**

EST or EPBD is a necessary papillary dilatation technique for CBD stone extraction. In DAPT cases, guidelines require DAPT reduction prior to EST. Although no reports have focused on EPBD in patients receiving DAPT, EPBD may be safe to perform on these patients, as there was no bleeding after EPBD in this study. If the hypothesis of this study is validated, it would lead to a reduction in the number of ERCPs, shorter hospital stays, and avoidance of an increased risk of embolism during the DAPT reduction period in CBD patients receiving DAPT. Prospective studies are needed to confirm our results and ensure evidence-based recommendations for EPBD in patients with DAPT.

**Abbreviations**

APAs, aspirin and antiplatelet agents; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation; JGES, Japan Gastroenterological Endoscopy Society; ASG, American Society for Gastrointestinal Endoscopy; ESGE, European Society for Gastrointestinal Endoscopy; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; ERCP, endoscopic retrograde cholangiopancreatography; Hb, hemoglobin; NSAIDs, nonsteroidal anti-inflammatory drugs; PEP, post-ERCP pancreatitis.

**Declarations**

**Ethics approval and consent to participate:** This retrospective observational study was reviewed and approved by the Institutional Review Board of Future Medical Research Center (IRB no. TGE02046-024). All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants included in the study by the opt-out method of our hospital website and in-hospital posting (as it was a retrospective study using information contained in medical charts and computerized records). This study was approved by our ethics committee.

**Consent for publication:** Not applicable.

**Availability of data and materials:** Technical appendix, statistical code, and dataset are available from the corresponding author upon request. No additional data are available for this study.
Competing interests: The authors declare that they have no competing interests.

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Authors’ contributions: SM and Kazuya K were the major contributors in writing the manuscript. SM, RJ, and AS analyzed and interpreted the patient data regarding bleeding risk after EST. SM, RJ, Kazuya K, MM, TN, KS, Karen K, CS, JK, CI, AS, Masahiro K, Makoto K, HU, and AS designed and initiated the study, enrolled patients, edited the paper, and approved the final version.

Acknowledgments

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References


**Figures**
Study population.

This retrospective study was conducted at the Shonan Kamakura General Hospital in Japan. Study enrollment commenced in May 2014 and ended in August 2022. This study included patients who underwent EPBD for bile duct stones and received DAPT or SAPT prior to EPBD. Patients who received warfarin or anticoagulant therapy were excluded from the study. Of the 134 patients enrolled, 103 were excluded based on the exclusion criteria. Finally, 31 patients were included in the analysis. Moreover, the number of patients underwent EPBD with DAPT therapy (DAPT group) was 9 (29%), while 22 (71%) underwent EPBD with SAPT (SAPT group).

CBD, common bile duct; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; EPBD, endoscopic papillary balloon dilation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile.docx