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Feasibility of endoscopic ultrasound-guided gallbladder drainage for acute cholecystitis patients receiving antithrombotic therapy

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Abstract

Background Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) as a treatment for patients with acute cholecystitis has been shown to obtain high technical and clinical success rates and a low recurrence rate. However, the safety of EUS-GBD for patients receiving antithrombotic therapy (ATT) has not been proven. The aim was to evaluate the safety and efficacy of EUS-GBD in patients receiving ATT.

Methods Twelve patients with acute cholecystitis associated with gallstones who were receiving antithrombotic therapy and underwent EUS-GBD were enrolled in this retrospective study. Patients with grade II or III cholecystitis who had failed endoscopic transpapillary GBD (ETGBD) or developed recurrence after multiple ETGBD procedures underwent urgent drainage by EUS-GBD. The primary outcome was the rate of bleeding complications after the procedure and the secondary outcomes were the technical and clinical success rates, complications, and recurrence.

Results Eleven (91.6%) patients underwent EUS-GBD with continuation of ATT (at least 1 agent). Five of 12 patients (41.7%) were receiving more than 1 agent for ATT. The rate of bleeding complications was 0% and the technical success rate was 100%, even though some patients had high-grade (severe) cholecystitis and/or several underlying diseases. Early complications were found in 2 (16.7%) patients. The clinical success rate was 91.7% (11/12). There were no recurrences of cholecystitis during the follow-up period (mean 261 [range 5-650] days).

Conclusions EUS-GBD yielded high technical and clinical success rates and a low recurrence rate. No patients receiving ATT developed bleeding complications. EUS-GBD might be a good option for patients on ATT.

Keywords Acute cholecystitis, antithrombotic therapy, endoscopic transpapillary gallbladder drainage, endoscopic ultrasound, percutaneous transhepatic gallbladder drainage

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Conflict of Interest: None

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Introduction

In the 2018 Tokyo Guidelines, the recommended first-line treatment for patients with moderate or severe acute cholecystitis is early laparoscopic cholecystectomy [1]. However, the surgical procedure can confer an increased risk of mortality on elderly patients who have many severe comorbidities [2,3]. In such cases, percutaneous transhepatic gallbladder drainage (PTGBD) is recommended as the alternative first-line treatment. Its technical and clinical success rates have been reported to be nearly 100% and 86-90%, respectively [1,4,5]. Endoscopic transpapillary GBD (ETGBD) is the second-line method for GBD in patients who should not undergo PTGBD because of massive ascites, an anatomically

inaccessible gallbladder, or the risk of self-removal of the drainage tube [1,6]. The technical and clinical success rates of ETGBD are 78-100% and 75-95%, respectively [5,7,8]. On the other hand, endoscopic ultrasound-guided GBD (EUS-GBD) is considered to be salvage treatment for patients who cannot undergo the other drainage methods, although the procedure has obtained high technical and clinical success rates of 84-93% and 92-97%, respectively [7,8].

Antithrombotic therapy (ATT) has been commonly used to prevent cardiovascular and cerebrovascular diseases in the elderly patients, and the risk of bleeding complications in this patient group should be considered with regard to most of the procedures used to treat biliary diseases [9,10]. Some guidelines allow PTGBD for patients receiving aspirin monotherapy [1,11]; however, the value and risk of adverse complications associated with the continuation of other antithrombotic agents and multiple agents during PTGBD are controversial [12,13]. Indeed, the risk of bleeding in PTGBD has been reported to be elevated, since the puncture procedure is performed through the highly vascular liver [13]. Because of its low risk of bleeding complications, ETGBD is recommended for patients receiving ATT or who have coagulopathy [1]; however, the evidence is limited [6], and the technical and clinical success rates of ETGBD are lower than those of EUS-GBD [7]. To the best of our knowledge, no study has evaluated the efficacy and complications, especially bleeding, associated with EUS-GBD in patients receiving ATT. Therefore, we aimed to investigate the safety and feasibility of EUS-GBD in patients with acute cholecystitis on ATT.

Patients and methods

Study design

Twelve patients with acute cholecystitis who were taking various antithrombotic agents and who underwent EUS-GBD between March 2017 and February 2019 at New Tokyo Hospital and Oita San-ai Medical Center were retrospectively analyzed in this study. Acute cholecystitis was diagnosed according to criteria based on clinical symptoms, signs of systemic inflammation, and computed tomography imaging [1,14]. Patients diagnosed with acute cholecystitis were classified by severity into 3 grades. According to the 2018 Tokyo Guidelines [14], patients with grade III (severe) and II (moderate) acute cholecystitis require urgent cholecystectomy or GBD. In accordance with the guidelines [1], ETGBD was first considered as an alternative to cholecystectomy or PTGBD because of the bleeding risk associated with ATT. Second, EUS-GBD was basically considered for patients whose ETGBD procedure had failed or who had developed frequent recurrent episodes of acute cholecystitis after ETGBD procedures. For some patients in whom ETGBD had failed, EUS-GBD was then performed during the same operation. Patients with cholecystitis accompanied by choledocholithiasis were excluded from this analysis, since for most of these patients cholecystitis resolves rapidly after endoscopic removal of the stone and therefore ETGBD is not needed.

EUS-GBD technique

An echoendoscope (GF-UCT260; Olympus, Tokyo, Japan) connected to the ultrasound scanner (ALOKA F-75; Hitachi Aloka medical, Tokyo, Japan) was used to detect the gallbladder from the stomach or duodenum. A 19-G needle for EUS-guided fine needle aspiration (EZ-shot 3 Plus; Olympus, Tokyo, Japan; Sonotip; Medicos Hirata, Osaka, Japan) was inserted into the gallbladder though the forceps channel of the echoendoscope. After the identification of bile by aspiration, a contrast agent was injected to identify the gallbladder fluoroscopically. The punctured tract was dilated along the inserted guidewire by a cautery dilator (Cyst-Gastro-Set; Century Medical, Tokyo, Japan; Fine-025; Medicos Hirata, Osaka, Japan) or a balloon dilator (Ren [4 mm diameter]; Kaneka, Yokohama, Japan). Subsequently, a 7-Fr double-pigtail plastic stent (PS) (Gadelius Medical Co, Tokyo, Japan), a fully covered dumbbell type metallic stent (MS) (M-Intraductal [10 or 8 mm diameter, 7 cm long]; Medicos Hirata), or a fully covered MS (Niti-S Biliary Covered Stent [10 mm diameter, 10 cm long]; Century Medical, Tokyo, Japan) was deployed to bridge the gallbladder and gastrointestinal cavity. All EUS-GBD procedures were performed by 3 expert endoscopists (RS, KH and HN) who had experience of performing more than 1000 screening EUS procedures and 10 EUS-GBD procedures.

Outcomes and definitions

The clinical backgrounds of the patients were evaluated, including the severity grade of cholecystitis and underlying diseases associated with ATT or coagulopathy. Underlying diseases included a medical history of heart disease, including atrial fibrillation, angina pectoris and myocardial infarction after percutaneous coronary intervention or surgery; non-cardiac vascular disease, including abdominal aortic aneurysm, cerebral infarction and peripheral arterial disease; and chronic kidney disease after introduction of dialysis. In this study, these underlying diseases were classified according to the American Society of Anesthesiologists (ASA) classification system [15].

Antithrombotic agents used by patients treated with EUS-GBD were analyzed. Antithrombotic agents included antiplatelet agents and anticoagulants. The antiplatelet agents consisted of aspirin (cyclooxygenase inhibitor), and clopidogrel and prasugrel (purinergic receptor antagonists). The anticoagulants consisted of warfarin (vitamin K epoxide reductase inhibitor), and dabigatran and apixaban (direct thrombin inhibitors).

Continuation or discontinuation of ATT during the procedure was analyzed. Discontinuation of ATT was performed according to the guidelines regarding the clinical use of antithrombotic agents during gastrointestinal endoscopy [16], and ATT was restarted the day after the procedure if no complications had occurred.

The primary outcome was the bleeding complication rate, while the secondary outcomes were the technical and clinical success rates and overall complication rate. Technical success rate was defined as the complete placement of the stent from gallbladder to digestive tract. Long-term clinical outcomes

of EUS-GBD, including recurrence of acute cholecystitis and late complications related to the EUS-GBD procedure or the inserted stent were also evaluated. Clinical success was defined as an improvement in cholecystitis without stent dysfunction within 14 days after the procedure. In addition, improvements in laboratory parameters of inflammation, including normalization of white blood cell count and a 50% reduction in C-reactive protein levels, were evaluated at 1, 3, and 6 days after the procedure. Early complications and stent dysfunction were defined as an event that occurred within 14 days after the procedure, while late complications and stent dysfunction were defined as an event that occurred 15 days or later after the procedure. The severity of complications was evaluated according to the classification by Cotton *et al* [17].

This study was approved by the Medical Ethics Committee at New Tokyo Hospital (Institutional Review Board No. 205) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Results

The clinical characteristics of the study patients are shown in Table 1. Their mean age was 80.3 (range 61-88) years, and 75% (9/12) were male. Grade III cholecystitis was identified in 33.3% (4/12) patients, while 16.7% (2/12) had coagulopathy with a prothrombin time-international normalized ratio of 1.5 or more. All patients had an underlying disease, and 50.6% (6/12) had many or overlapping diseases. All the patients had ASA grade III scores. Table 2 shows the agents used for ATT. Multiple agents were used by 41.7% (5/12) patients, and 91.6% (11/12) patients underwent EUS-GBD while continuing at least 1 agent for ATT. One patient underwent the procedure after ATT was stopped. Table 3 lists the procedure-related factors and therapeutic outcomes of the EUS-GBD procedure. The rate of bleeding complications was 0%. The technical success rate was 100%, even though some patients had higher than moderate-grade cholecystitis and/or multiple underlying diseases. The postoperative course of patients was good, except for 1 fatality, and the clinical success rate was 91.7%.

Early complications occurred in 16.7% (2 of 12) of patients. One patient with peritonitis recovered with conservative treatment. However, another patient with gallbladder perforation died of an acute myocardial infarction 5 days after the procedure, since he could not take an oral antithrombotic agent for atrial fibrillation that occurred 3 days after the ESU-GBD procedure.

Stent migration to the digestive tract occurred in 3 patients 6 months or more after the procedure, without clinical symptoms or the recurrence of cholecystitis. There were no recurrences of cholecystitis during the follow-up period (mean 261 [range 5-650] days) in all patients. Table 4 lists factors possibly associated with the early complication; however, there was no specific association.

Table 1 Clinical characteristics of enrolled patients

Characteristics	Value
Mean age ± SD (years)	80.3±8.3
Male sex, n (%)	9 (75)
Severity grade of cholecystitis	
Moderate: grade II, n (%)	8 (66.7)
Severe: grade III, n (%)	4 (33.3)
WBC count, mean ± SD ($\times 10^3/\mu L$)	14.4±5.6
CRP concentration, mean ± SD (mg/dL)	13.3±8.6
PT-INR	1.4 (1.1-3.0)
Underlying disease, n (%)	12 (100)
Heart disease, n (%)	4 (33.3)
Non-cardiac vascular disease, n (%)	8 (66.7)
Chronic kidney disease	2 (16.7)
ASA grade III	12 (100)

ASA, American Society of Anesthesiologists; ATT, antithrombotic therapy; CRP, C-reactive protein; PT-INR, prothrombin time-international normalized ratio; SD, standard deviation; WBC, white blood cells

Discussion

None of the patients in this study developed a bleeding complication during or after their EUS-GBD procedure, although most of these patients with acute cholecystitis were treated by EUS-GBD while continuing ATT, a possible risk factor for bleeding in this situation. In addition, the technical

Table 2 Agents used for ATT before and during the procedure

Agents	No. of patients (%)
DAPT/ DOAC/ Both user	10 (83.3) / 4 (33.3) / 2 (16.7)
ATT used before the procedure	
One agent/two	7 (58.3) / 5 (41.7)
Continued ATT during the procedure	11 (91.6)
Continued ATT; one agent/two, n/N (%)	8/11 (72.7) / 3/11 (27.3)

ATT, antithrombotic therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants

Table 3 Procedure-related factors and therapeutic outcomes of EUS-GBD

Factors	Value
Bleeding complication rate, n (%)	0 (0)
Technical success rate, n (%)	12 (100)
Procedure length, mean (range) (min)	19.7 (7-68)
Early complication rate, n (%)	2 (16.7)
Normalization of WBC 6 days after the procedure, n (%)	8 (66.7)
Normalization of CRP 6 days after the procedure, n (%)	8 (66.7)
Clinical success rate, n (%)	11 (91.7)
Follow-up period (range) (days)	261 (5-650)
Late complication rate, n (%)	1 (8.3)
Recurrence rate, n (%)	0 (0)

EUS-GBD, endoscopic ultrasound-guided gallbladder drainage; CRP, C-reactive protein; WBC, white blood cells

Table 4 Factors related to the complication

Patient No. (Age/Sex)	Severity of cholecystitis	Puncture site	Stent type	Procedure length (min)	Antithrombotic agents	Continued agents	Early complication	Late complication	Bleeding
1 (75/M)	II	Stomach	7Fr 12cm PS	18	Clopidogrel, aspirin	Clopidogrel	None	None	None
2 (88/M)	II	Stomach	MS	16	Aspirin	Aspirin	None	None	None
3 (61/M)	II	Duodenum	Dumbbell MS	17	Aspirin, prasugrel	Aspirin, prasugrel	None	None	None
4 (70/F)	III	Duodenum	Dumbbell MS	18	Clopidogrel	None	None	None	None
5 (76/M)	III	Duodenum	Dumbbell MS	68	Aspirin, warfarin	Aspirin	None	None	None
6 (85/F)	II	Duodenum	Dumbbell MS	18	Clopidogrel	Clopidogrel	None	None	None
7 (83/M)	II	Duodenum	Dumbbell MS	18	Warfarin	Warfarin	Peritonitis	None	None
8 (82/M)	III	Duodenum	Dumbbell MS	10	Aspirin, warfarin	Aspirin, warfarin	Perforation, AMI	NA	None
9 (86/F)	III	Duodenum	Dumbbell MS	9	Aspirin	Aspirin	None	Ulcer	None
10 (84/M)	II	Stomach	Dumbbell MS	25	Aspirin, prasugrel	Aspirin, prasugrel	None	None	None
11 (87/M)	II	Duodenum	Dumbbell MS	12	Apixaban	Apixaban	None	None	None
12 (87/M)	II	Duodenum	Dumbbell MS	7	Clopidogrel	Clopidogrel	None	None	None

MS, metallic stent; NA, no assessment; PS, plastic stent; AMI, acute myocardial infarction

success rate was 100%. Thus, EUS-GBD could be allowed for patients who require the continuation of ATT. The EUS-GBD procedure has shown high technical and clinical success rates of 84-93% and 92-97%, respectively [7,8,18]. Compared with PTGBD, EUS-GBD with a lumen-apposing MS (LAMS) has shown high technical and clinical success rates (technical: 98% vs. 100%, P=0.88; clinical: 96% vs. 91%, P=0.20, respectively). In addition, the mean number of repeat interventions per patient was 0.2±0.4 vs. 2.5±2.8 repeats, respectively (P<0.01) [19]. Another investigator also reported that the technical and clinical success rates and recurrence rates of EUS-GBD compared to ETGBD were as follows: technical: 99% vs. 87% (P<0.01), clinical: 99% vs. 86% (P<0.01) and recurrence: 3.2% vs. 12.4% (P=0.04), respectively [20]. Other comparative studies have reported that EUS-GBD obtained similar or higher technical and clinical success rates and lower recurrence rates compared to the other drainage procedures [7,21].

PTGBD has been associated with several complications such as bleeding, pneumothorax, biloma, and biliary peritonitis [6]. PTGBD has also shown overall complication rates as high as 14% [6], rates of recurrence within 1 year of 10-20%, and a mortality rate of up to 15.4% for poor surgical candidates [4]. In addition, patients with dementia show a risk of stent self-removal associated with postprocedural pain and discomfort [22-24]. On the other hand, the reported early and late complication rates of ETGBD are 6.3% and 5.5%, respectively [25]. These included pancreatitis due to the endoscopic retrograde cholangiopancreatography procedure; cystic duct perforation due to the guidewire or cannulation; cholangitis; abscess; duodenal ulcer; gastrointestinal perforation; and stent dysfunction, migration, and occlusion [25]. The reported early and late complication rates of EUS-GBD are 7.0% and 4.4%, respectively, similar to the rates of ETGBD [25]. These complications included pneumoperitoneum; peritonitis; perforation; migration at stent placement; bile fluid collection; bleeding; pancreatic infection; abscess; and stent dysfunction, migration, and occlusion. The complications of EUS-GBD are rarely fatal, in contrast to some complications of PTGBD [25].

With regard to the complications associated with these procedures, associated bleeding should be discussed thoroughly with patients on ATT. Currently, the prevention of cardiovascular or cerebrovascular thromboembolism, which have serious or fatal outcomes, is thought to be more important than bleeding complications. In our study, 1 patient with gallbladder perforation died of acute myocardial infarction that might have been the result of the discontinuation of ATT. Therefore, antiplatelet medications, at least aspirin monotherapy, should be continued during therapeutic procedures for patients who have a high risk of thromboembolism [9,10]. Guidelines have allowed PTGBD for patients with acute cholecystitis and continued aspirin monotherapy during the procedure [1,11], although a bleeding complication after PTGBD was one of the most notable complications because of the needle puncture through the liver. The rate of severe bleeding after the procedure has been reported to be as high as 4.7% [12]. However, whether or not the bleeding risk of PTGBD increases for patients receiving ATT remains unclear [12,26,27].

Although the evidence was limited, ETGBD was recommended as the first-line GBD procedure for patients receiving ATT [1,6]. Guidelines from the Japan Gastroenterological Endoscopy Society (JGES) [16], the American Society for Gastrointestinal

Endoscopy (ASGE) [28], and the European Society for Gastrointestinal Endoscopy (ESGE) [29] consider the use of ETGBD without endoscopic sphincterotomy (EST) to be a low-bleeding-risk procedure and do not require the discontinuation of any type of antithrombotic agent [16,28-30]. The bleeding complication rate of ETGBD was reported to be 0-8.3%, though most studies showed 0% [6,21-35]. Only a single study on ETGBD for patients receiving ATT reported a bleeding complication rate of 0% [6]. One review found an overall rate of bleeding complications of 0.65% (9/1374) [25].

On the other hand, the guidelines from medical societies require that EUS-GBD should be performed with discontinuation of all types of ATT, since the procedure has shown a high risk of bleeding. The ASGE has recommended that EUS-GBD should be performed with the continuation of aspirin monotherapy only; however, the JGES and ESGE have recommended aspirin monotherapy only for patients who have a high risk of thromboembolism. This decision was based on the evidence of the bleeding risk of EUS-guided fine-needle aspiration (EUS-FNA), classified as a high-bleeding-risk procedure [29]. These guidelines did not refer to the available data on EUS-FNA performed for patients on continued ATT. EUS-FNA for patients with and without discontinuation of ATT showed bleeding rates of 0.2-1% and 0.4-2.4%, respectively [36-38]. One study reported a low bleeding rate even in patients who underwent EUS-FNA on continued aspirin or cilostazol [36]. The others reported a slight increase in the bleeding risk of patients receiving ATT, although no patients developed severe bleeding or thromboembolism [37,38]. Thus, EUS-FNA and related procedures for patients on ATT would only be allowed for patients who have a high risk of thromboembolism. Regarding EUS-GBD, the reported rates of overall bleeding complications were 0-12.5% [25,39-41], while a systematic review on the complications of EUS-GBD with LAMS revealed a 4.6% rate of bleeding complications occurring both early and late [42]. Moreover, with regard to bleeding complications, EUS-GBD may be safer to perform than PTGBD, because the gastrointestinal tract is less vascular than the liver [22,43].

Also with regard to bleeding complications, ETGBD might be feasible for patients receiving ATT. However, the technical success rate of ETGBD has been lower, and the recurrence rate higher than those rates obtained with EUS-GBD [20,25]. In our study, none of the 12 patients who had been on ATT and underwent EUS-GBD developed bleeding complications, although 11 patients underwent the procedure without discontinuation of their ATT. However, 1 of our patients, who had not received ATT before EUS-GBD, developed a late bleeding complication. That patient was not included in this analysis; however, it was an instructive case. The patient was initially administered apixaban 3 days after EUS-GBD because of paroxysmal atrial fibrillation, and massive bleeding from the gallbladder occurred 18 days after the procedure. The bleeding originated from contact injury to the gallbladder wall by a MS; therefore, the stent was changed to a plastic one to prevent the bleeding. Thus, patients on ATT should be placed in intensive care after the EUS-GBD procedure. Moreover, in our cases, a self-expandable MS with relatively long and rough shape was used; therefore, the complications of bleeding and gallbladder perforation might be potentially more likely compared with another study that used LAMS with a short and smooth shape [44]. With the current guidelines, ETGBD is the only recommended procedure for patients receiving ATT. However, EUS-GBD should be performed for patients on ATT whose ETGBD has failed or who develop frequent recurrences of acute cholecystitis after ETGBD. For the future, improved devices, further developments, and education of endoscopists should lead to a safer EUS-GBD procedure, which should thus be considered not as a salvage treatment but also as an approved option for the drainage of acute cholecystitis.

This study has limitations. First, it was a preliminary study of EUS-GBD for patients receiving ATT, and therefore a small number of patients were enrolled. A larger multicenter study is needed. Second, EUS-GBD procedures were only performed by skilled pancreatobiliary endoscopists. The education and learning curve of endoscopists regarding this procedure should also be examined.

In conclusion, EUS-GBD obtained high rates of technical and clinical success with a low recurrence rate. None of the patients on continued ATT developed bleeding complications. EUS-GBD might be a preferred alternative choice for GBD in patients on ATT after failed ETGBD.

Summary Box

What is already known:

- Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) as a treatment for patients with acute cholecystitis has shown high technical and clinical success rates
- However, the safety of EUS-GBD for patients receiving antithrombotic therapy (ATT) has not been proven

What the new findings are:

- Eleven (91.6%) of 12 patients underwent EUS-GBD with continuation of ATT, and 5 patients (41.7%) were receiving one or more antithrombotic drug
- After EUS-GBD for these patients, the rate of bleeding complications was 0% and the technical success rate was 100%
- No recurrences of cholecystitis occurred in patients who underwent EUS-GBD during the follow-up period (mean 261 [range 5-650] days)
- Therefore, EUS-GBD may be a good option for patients on ATT

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