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Feasibility, Efficacy, and Predictive Factors for the Technical Success of Endoscopic Nasogallbladder Drainage: A Prospective Study

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See editorial on page 141.

Background/Aims: Several studies have shown the usefulness of endoscopic nasogallbladder drainage (ENGBD) in patients with acute cholecystitis. However, the procedure is difficult, and factors that affect technical success have not yet been clarified. We conducted a prospective study to evaluate the technical feasibility, efficacy, and predictive factors for the technical success of ENGBD in patients with acute cholecystitis. **Methods:** All patients with moderate or severe acute cholecystitis who were enrolled underwent ENGBD between April 2009 and April 2011. Patients with surgically altered anatomy or pancreatobiliary malignancies were excluded. The primary outcomes included technical success, clinical success, and complications. Factors that could affect the technical success were also examined. **Results:** Of the 27 patients who underwent ENGBD during the study period, technical success was achieved in 21 (78%) and clinical improvement was achieved in 20 (95%). Early complications were encountered in four patients (15%). Gallbladder wall thickness (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.08 to 2.47) and age (OR, 1.16; 95% CI, 1.00 to 1.35) were effective predictors of technical failure. **Conclusions:** ENGBD was effective in resolving acute cholecystitis; however, this modality was technically challenging and had a limited success rate. Because of technical difficulties, ENGBD should be reserved for limited indications. **(Gut Liver, 2015;9:239-246)**

Key Words: Acute cholecystitis; Endoscopic retrograde cholangiopancreatography; Gallbladder drainage

INTRODUCTION

Although early laparoscopic cholecystectomy is used for the primary management of acute cholecystitis,[1,2] in critically ill patients, cholecystectomy is associated with increased morbidity and mortality rates.[3,4] Therefore, elective cholecystectomy after initial management with percutaneous or endoscopic drainage may be preferable for patients with extensive local inflammation or high risk for emergency cholecystectomy because of their critical illness or underlying medical condition.[5-7] In the updated Tokyo guidelines 2013 (TG13) management bundles, for patients with Grade II (moderate) and III (severe) acute cholecystitis at high surgical risk, immediate biliary drainage is recommended. Furthermore, for Grade II patients, immediate biliary drainage or drainage if no early improvement along with the initial treatment is recommended.[8]

Percutaneous transhepatic gallbladder drainage (PTGBD) is the most widely established among various gallbladder drainage methods.[5] However, the application of this procedure is difficult because it cannot be performed in the presence of severe coagulopathy, thrombocytopenia, or at an anatomically inaccessible location. Additionally, PTGBD can result in bile leakage, hemorrhage, pneumothorax, and catheter displacement.[9]

Endoscopic nasogallbladder drainage (ENGBD) has been proposed as an alternative therapy to PTGBD more than 20 years ago.[10-18] Despite this, ENGBD remains technically challenging, and information regarding its success rates and clinical outcomes in large-scale, prospective studies is required. Most of these previous studies either had a retrospective study design or included small patient samples. The reported technical success rates of ENGBD are 64% to 89%, which are lower than those reported for the percutaneous approach and for difficult cases.

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However, the factors that affect the technical difficulty of the procedure remain unclear.

Our study was designed to prospectively evaluate the technical feasibility, efficacy, and factors that predict the technical success of ENGBD in patients with acute cholecystitis.

MATERIALS AND METHODS

1. Patients

This prospective, nonrandomized, single-center study was conducted between April 2009 and April 2011 and included all patients with moderate or severe acute cholecystitis diagnosed according to the Tokyo Guidelines for assessing and grading of acute cholecystitis.[19] The inclusion criteria were age >20 years and the presence of moderate or severe acute cholecystitis. Patients with surgically altered anatomy (Billroth-II gastrectomy, Roux-en-Y gastrectomy, pancreaticoduodenectomy, or hepaticojejunostomy), acute cholangitis, or bile duct stone, and pancreatobiliary malignancies were excluded from the study. Intravenous cefmetazole was initiated after the diagnosis of acute cholecystitis and was continued until the cholecystitis resolved. All patients provided written informed consent to participate and undergo the procedure in this study. The Institutional Review Board of our hospital approved this study.

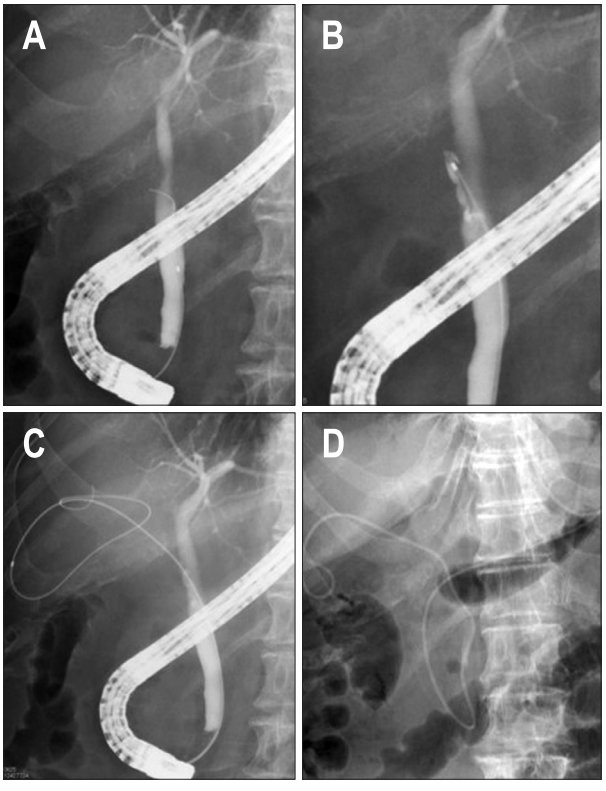


Fig. 1. Fluoroscopic endoscopy images of nasogallbladder drainage. (A) The catheter is inserted into the bile duct, and a 0.035-inch hydrophilic guide wire is advanced into the cystic duct. (B) An endoscopic retrograde cholangiopancreatography catheter is inserted into the cystic duct. (C) Once the guide wire has formed generous loops in the gallbladder, the catheter is advanced, and the bile is aspirated to confirm the position of the wire. (D) The wire is replaced with a stiff-type wire, and a 5-F pigtail-type nasobiliary drainage tube is inserted and left to dwell in the gallbladder.

2. Endoscopic procedures

Endoscopic procedures were mainly performed by physicians with extensive experience in endoscopic retrograde cholangiopancreatography (ERCP) using a side-viewing duodenoscope (JF-260V or TJF-260V; Olympus Medical Systems, Tokyo, Japan) and a catheter (ERCP-Katheter; MTW Endoskopie, Wesel, Germany) or a sphincterotome (CleverCut 3V^{TM}; Olympus Medical Systems). Biliary sphincterotomy was performed in necessary cases. Following cholangiography, a 0.035-inch or 0.025-inch hydrophilic guide wire (Radifocus; Terumo, Tokyo, Japan) was advanced into the gallbladder via the cystic duct. When the cystic duct was not visualized on cholangiography, the cystic duct entry was located by moving quickly up and down with rotation the hydrophilic guide wire preceding the catheter which is positioned at the bottom of the bile duct. Subsequently, the catheter was advanced carefully to the cystic duct following the guide wire. If cystic duct negotiation was unsuccessful because of distribution or deformation, a catheter with a flexible tip (Swing-tip; Olympus Medical Systems) was used. Following successful gallbladder cannulation, the hydrophilic guide wire was replaced with a stiff type guide wire (Jagwire®, Boston Scientific, Natick, MA, USA; or VisiGlide, Olympus Medical Systems). After withdrawing the catheter, a 5-F pigtail-type nasobiliary drainage tube was inserted into the gallbladder (Fig. 1).

3. Follow-up

After the procedure, clinical symptoms and physical findings were recorded. If viscous pus was aspirated, the gallbladder was irrigated with normal saline. Laboratory data were also assessed the following day and after 3 and 7 days. In principle, laparoscopic cholecystectomy was performed as soon as practicable after improvement of the gallbladder inflammation. The drainage tube was left in place until surgery. However, if the patients refused early surgery, the drainage tube was removed.

4. Study end points and definition of events

The primary endpoint of the study was the feasibility and efficacy of ENGBD for acute cholecystitis. Technical success was defined as adequate placement of the drainage tube. To determine the predictive factors that affect technical success, the following parameters were evaluated: age, gender, cause of cholecystitis (calculous or acalculous), severity grade of cholecystitis, laboratory features (white blood cell [WBC] count and C-reactive protein [CRP] level), use of anticoagulation or antiplatelet drugs, gallbladder wall thickness, major/minor axis length of the gallbladder, number of gallstones (single/multiple), diameter of gallstones, impaction of a stone in the cystic duct or

gallbladder neck, cystic duct visualization by cholangiography, diameter of the common bile duct (CBD), and direction of the cystic duct. Clinical improvement was defined as normalization of the clinical parameters of acute cholecystitis, such as abdominal pain, fever, and leukocytosis. Complications were defined as any adverse event occurring during or after the procedure;[20] all complications were recorded prospectively. Because all ENGBD procedures were performed in hospitalized patients, the period until oral intake was used as the basis for evaluating the severity of complications, instead of the length of hospital stay.

5. Statistical analysis

Categorical variables were examined using the Fisher exact test. Continuous variables were examined using the Student t-test. A p-value of <0.05 was considered to indicate a statistically significant difference. Multivariate stepwise analysis was performed with the backward elimination method to obtain an efficient predictive model. A receiver operating characteristic (ROC) curve was constructed to set cutoffs of continuous variables. To make a diagnostic tree, the first branch was based on a variable showing the highest product of sensitivity and specificity. The second branch was chosen in the same manner as the first branch.

All statistical analyses were performed using EZR (Jichi Medical University Saitama Medical Center, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[21] SPSS statistics 20 (IBM Corp., Armonk, NY, USA) was also used.

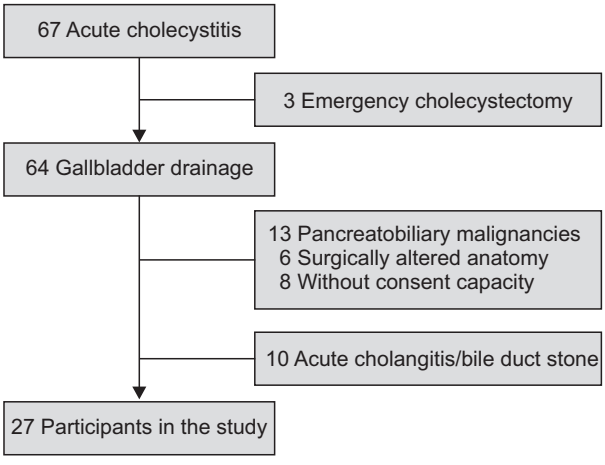


Fig. 2. Patient disposition.

RESULTS

From April 2009 to April 2011, five patients with severe acute

Table 1. Patient Baseline Characteristics

Characteristic	Value
No. of patients	27
Sex, male/female	12/15
Age, mean±SD, yr	65.6±15.2
Type of cholecystitis	
Calculous	24
Acalculous	3
Severity grade of cholecystitis	
Moderate (grade II)	27
Severe (grade III)	0
Laboratory features	
White blood cells, mean±SD, $\times 10^3/\mu L$	13.0±4.7
C-reactive protein, mean±SD, mg/dL	18.1±10.5
Use of anticoagulation drugs or antiplatelet drugs	
Yes	7
No	20

All values are presented as the number of patients per category, except where indicated.
SD, standard deviation.

Table 2. Summary of Results

Variable	Value
Technical success	78 (21/27)
Procedure time, mean±SD, min	35.5±19.9
Clinical success	95 (20/21)
Duration of clinical success, mean±SD, day	2.3±1.0
Complications	15 (4/27)

All values are presented as % (no./total no.), except where indicated.
SD, standard deviation.

Table 3. Complications

	Complication	Successful ENGBD	Grade	Clinical symptoms	Further intervention
1	Pancreatitis	Yes	Mild	Abdominal pain	-
2	Cystic duct injury	Yes	Mild	Abdominal pain	-
3	Cystic duct injury	No	Moderate	None	PTGBD, ENBD
4	Cystic duct injury	No	Moderate	None	PTGBD, ENBD

ENGBD, endoscopic nasogallbladder drainage; PTGBD, percutaneous transhepatic gallbladder drainage; ENBD, endoscopic nasobiliary drainage.

cholecystitis and 62 patients with moderate acute cholecystitis were treated at our center. Of these patients, two patients (i.e., one with severe and one with moderate acute cholecystitis) underwent urgent laparoscopic cholecystectomy because of gallbladder perforation and were therefore excluded from the study. One patient with moderate acute cholecystitis and a diagnosis of necrotizing cholecystitis with emphysema, who underwent urgent laparoscopic cholecystectomy, was excluded. Of the 64 patients who were not candidates for emergency surgery, 37 (i.e., four with severe and 33 with moderate acute cholecystitis) were excluded from the present study because of pancreatobiliary malignancies (13 patients), acute cholangitis or bile duct stone (10 patients), surgically altered anatomy (six patients), and without consent capacity (eight patients). Overall, 27 patients (12 men, 15 women; mean age, 65 years; range, 39 to 86) who met the inclusion criteria were enrolled (Fig. 2). The clinical characteristics of the 27 study patients are summarized in Table 1. Most patients had epigastric pain and fever. Laboratory tests revealed leukocytosis (mean WBC count, 13.0±4.7 [$\times 10^3/\mu L$], mean±standard deviation [SD]) or elevated CRP levels (mean, 18.1±10.5 mg/dL). None of the patients had apparent organ dysfunction. In 25 patients (93%), a single or multiple gallstones were identified by transabdominal ultrasound or computed tomography.

Procedure outcomes are shown in Table 2. The mean procedure time was 35.5 minutes. Technical success was achieved in 21 of the 27 patients (78%). ENGBD failed in six patients because of the inability to pass the guide wire into the cystic duct and gallbladder; in these cases, we performed PTGBD. Clinical improvement was achieved in 20 of the 27 patients (intention-to-treat: 74%, per-protocol: 95%) after a mean duration of 2.3 days. Of the 21 patients showing technical success, 15 patients underwent subsequent elective surgery with drainage tube indwelling. In six patients, the drainage tube was removed after resolution of acute cholecystitis. One patient showed relapse of acute cholecystitis 23 days after removal of the drainage tube and the patient underwent urgent cholecystectomy. There was no recurrence of acute cholecystitis in four patients. A total of 20 patients underwent elective cholecystectomy, which included two patients having acalculous cholecystitis with a thick gallbladder wall and intramural abscess. In the remaining patient who had a severe comorbid disease, cholecystectomy was not performed. The patient was followed up at another hospital. Unfortunately, the long-term outcome is unknown. Complications were encountered in four of the 27 patients (15%), including cystic duct injury (three patients) and mild post-ERCP pancreatitis (one patient) (Table 3). In all patients with cystic duct injury, the hydrophilic guide wire penetrated through the cystic duct wall. ENGBD was completed in one patient. However, in the other two patients, ENGBD was unsuccessful. These patients were treated by PTGBD with endoscopic nasobiliary drainage. The prolongation periods of hospital stay were 0, 2,

Table 4. Characteristics of Six Patients Who Experienced Technical Failure

	Age, yr/sex	Type of cholecystitis	Severity grade	WBC, $\times 10^3/\mu L$	CRP, mg/dL	GB wall Thickness, mm	Major axis length, mm	Minor axis length, mm	No. of stone	Stone diameter, mm	Impaction of stone in the cystic duct or GB neck	CBD diameter, mm	Cystic duct visualization	Direction of cystic duct
1	65/F	Calculous	Moderate	5,740	22.61	8	82	35	Single	4	Yes	10	No	Upper side
2	82/F	Calculous	Moderate	23,420	22.44	13	113	40	Multiple	23	No	11	No	Upper side
3	64/M	Calculous	Moderate	9,780	38.51	13	58	43	Multiple	14	No	9	Yes	Lower side
4	80/F	Calculous	Moderate	15,370	27.63	12	108	38	Multiple	5	Yes	16	Yes	Lower side
5	81/F	Calculous	Moderate	15,400	44.55	8	77	38	Single	14	No	12	No	Lower side
6	81/F	Calculous	Moderate	11,150	10.81	9	85	42	Multiple	13	No	6	No	Lower side

WBC, white blood cells; CRP, C-reactive protein; GB, gallbladder; CBD, common bile duct; F, female; M, male.

and 2 nights. Post-ERCP pancreatitis was resolved by conservative therapy, and the prolongation of hospital stay was 2 nights. There were no procedure-related deaths.

The characteristics of all the patients with technical failure are summarized in Table 4. All the patients are more than 60 years of age, with four patients being 80 years of age or older. The gallbladder wall thickness in all the patients was more than 7 mm, and it was more than 10 mm in the three patients. The CRP level was more than 20 mg/dL in five patients. The CBD diameter was more than 8 mm in five patients. The direction of the cystic duct was towards the lower side in four patients.

Table 5. Factors Associated with the Technical Failure of Endoscopic Nasogallbladder Drainage: Univariate Analysis

Variable	ENGBD success (n=21)	ENGBD failure (n=6)	p-value
Sex, male/female	11/10	1/5	0.182
Age, yr	62.8±15.6	75.5±8.5	0.069
White blood cells, $\times 10^3/\mu L$	12.9±4.4	13.4±6.0	0.818
C-reactive protein, mg/dL	15.3±8.4	27.7±12.1	0.008
Gallbladder wall thickness, mm	5.9±3.7	10.5±2.4	0.009
Major axis length, mm	95.4±19.0	87.1±20.4	0.365
Minor axis length, mm	42.8±8.4	39.3±2.9	0.329
Gallstone no., single/multiple	9/9	4/2	0.649
Gallstone diameter, mm	11.3±8.3	12.1±6.9	0.836
Stone impaction in the cystic duct or gallbladder neck, yes/no	10/11	2/4	0.661
Cystic duct visualization by cholangiography, yes/no	7/14	2/4	1
Common bile duct diameter, mm	7.4±2.3	10.6±3.3	0.011
Cystic duct direction, upper right side/other side	17/4	2/4	0.044

All values are presented as the means±SD, except where indicated.
ENGBD, endoscopic nasogallbladder drainage.

Table 6. Factors Associated with the Technical Failure of Endoscopic Nasogallbladder Drainage: Multivariate Stepwise Analysis

Variable*	p-value	OR	95% CI
Wall thickness (per 1 mm increase)	0.020	1.64	1.08–2.47
Age (per 1 yr increase)	0.045	1.16	1.00–1.35

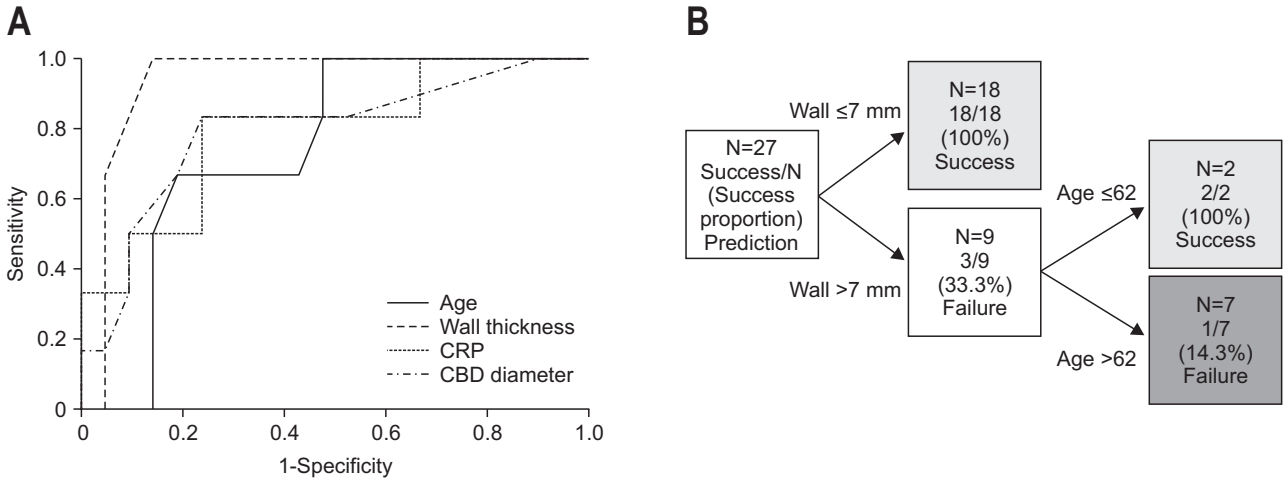
OR, odds ratio; CI, confidence interval.
*At the first step, age, common bile duct diameter, C-reactive protein, sex, and cystic duct direction were included. These factors were associated with endoscopic nasogallbladder drainage failure (p<0.2 in the univariate analysis) and were regarded as potential predictors. Multivariate stepwise (backward elimination method-the Wald method) analyses were then performed to obtain an efficient predictive model.

Univariate analysis for possible predictive factors indicated that CRP level (p=0.008), gallbladder wall thickness (p=0.009), CBD diameter (p=0.011), and cystic duct direction (p=0.044) were statistically significant predictors for technical failure (Table 5). To obtain an efficient predictive model, multivariate stepwise analyses were performed by the backward elimination method (Wald method) including the factors with p-value <0.2 on the univariate analysis, which were considered as potential predictors. The analysis identified that the model with gallbladder wall thickness (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.08 to 2.47) and age (OR, 1.16; 95% CI, 1.00 to 1.35) was an efficient predictive model for technical failure in ENGBD in this study (Table 6).

For a more practical application, we attempted to construct a diagnostic tree for the prediction of technical failure. We initially selected four factors that were significantly associated with ENGBD failure on the univariate analysis. Because these four factors were continuous variables, we performed ROC analysis to set optimal cutoffs (Fig. 3A). Because wall thickness resulted in a high AUC, 100% sensitivity, and high specificity (Fig. 3B), it was selected as the first branch of the tree. The second branch was based on age because the highest product of sensitivity and specificity was observed. The diagnostic tree based on the combination of wall thickness and age demonstrated a sensitivity of 100% and a specificity of 95.2% (Fig. 3C). These results are consistent with those of the multivariate stepwise analysis.

DISCUSSION

Early laparoscopic cholecystectomy is the standard treatment of choice for acute cholecystitis.[1,2] However, in elderly patients with underlying severe comorbidities such as liver cirrhosis or cardiopulmonary disease, cholecystectomy is associated with increased morbidity and mortality rates.[3,4] Furthermore, highly experienced surgeons, anesthesiologists, and medical staff, and a well-equipped facility are crucial requirements for an emergency laparoscopic cholecystectomy.[13] Most institutes lack these staff and facility; in such cases, early or urgent gallbladder drainage is a useful temporary measure for gallbladder decompression. As per the Tokyo guidelines, PTGBD, percutaneous transhepatic gallbladder aspiration (PTGBA), and ENGBD are recommended as nonsurgical gallbladder drainage methods.[7] Thus far, PTGBD has been the most commonly used method. However, it is not suitable in patients with severe coagulopathy, thrombocytopenia, or an anatomically inaccessible gallbladder location. Furthermore, its morbidity rate varies from 4% to 19% because of complications such as hemorrhage, pneumothorax, and catheter displacement.[6,9,22-24] PTGBA is an easy, low-cost bedside-applicable procedure without the patient discomfort or risk of catheter displacement seen in PTGBD. However, the drainage effect of single PTGBA is lower than that of PTGBD as described in a randomized controlled trial.[25] On the other hand,



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	AUC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	p-value*
Age	0.746 (0.553-0.939)	>62	1.000 (0.547-1.0)	0.524 (0.298-0.743)	0.054
Wall thickness	0.937 (0.839-1.0)	>7	1.000 (0.547-1.0)	0.857 (0.637-0.970)	<0.001
CRP	0.794 (0.584-1.0)	>20	0.833 (0.359-0.996)	0.772 (0.528-0.918)	0.015
CBD diameter	0.794 (0.575-1.0)	>8	0.833 (0.359-0.996)	0.772 (0.528-0.918)	0.015

Fig. 3. Receiver operating characteristic analysis and diagnostic tree. (A, B) Receiver operating characteristic analysis to set optimal cutoffs. (C) Diagnostic tree based on the combination of wall thickness and age.
CRP, C-reactive protein; CBD, common bile duct; AUC, area under the curve; CI, confidence interval.

Table 7. Outcomes of Endoscopic Nasogallbladder Drainage (No. of Cases, >10)

Author	Year	Type of study	No. of cases	Technical success, %	Clinical success, %	Complications, %
Feretis *et al.*[10]	1993	R	18	89	89	0
Nakatsu *et al.*[12]	1997	R	21	81	81	0
Toyota *et al.*[13]	2006	R	22	82	82	0
Kjaer *et al.*[14]	2007	R	34*	71	62	9
Itoi *et al.*[15]	2008	R	43	84	81	0
Ogawa *et al.*[16]	2008	R	11	64	64	0
Mutignani *et al.*[17]	2009	R	35*	83	69	11
Present series		P	27	78	74	15

R, retrospective; P, prospective.
*Including endoscopic gallbladder stenting cases.

ENGBD can be used for patients with severe coagulopathy or thrombocytopenia, particularly those with end-stage liver disease. ENGBD has also been reported as an alternative treatment procedure in patients in whom the percutaneous approach is difficult to perform.[10-18] However, a shortcoming of this procedure is that most of the reports demonstrating the feasibility and efficacy of ENGBD have been based on results of retrospective studies (Table 7). Consequently, there may be selection bias. Therefore, we conducted a prospective clinical study to clarify the feasibility and clinical efficacy of ENGBD for acute cholecystitis. In this clinical study, univariate analysis revealed the following statistically significant possible predictive factors for technical failure: CRP, gallbladder wall thickness, CBD diameter, and cystic duct direction. Furthermore, on the multivariate stepwise analysis, gallbladder wall thickness and age were found to be significant predictive factors. The diagnostic tree based on

the combination of wall thickness and age demonstrated a sensitivity of 100% and a specificity of 95.2%. One of the causes of technical failure may be the difficulty in negotiation and passage through the cystic duct using a guide wire. Theoretically, the cystic duct direction may cause technical difficulty during cystic duct negotiation and cannulation. Cannulation is relatively easy if the cystic duct is located on the upper right side of the bile duct. In contrast, guide wire or catheter manipulation is difficult if the cystic duct is located on the left or lower side. In this study, univariate analysis showed that cystic duct direction is a possible predictive factor for technical failure. However, based on the multivariate analysis, this factor was not statistically significant for technical failure. This inconsistent result may be due to the small sample size of the study. In contrast, acute cholecystitis associated with a thick gallbladder wall may make cystic duct cannulation more difficult owing to inflammation. Furthermore, the reason why age may affect technical failure is not clear from the present results. However, it is possible that the endoscopic procedure was abandoned earlier in elderly patients than in young patients because of their general condition.

From the present results, the clinical improvement rate by ENGBD in patients with acute cholecystitis was high. ENGBD is a difficult procedure to perform. In the present study, although the procedure was performed or supervised by experienced endoscopists, the technical success rate was insufficient. Therefore, we believe that this procedure should be performed only in a well-equipped tertiary-care center with experienced endoscopists and medical staff. Based on our findings, we do not recommend ENGBD as the first-choice treatment for gallbladder drainage in patients with thick gallbladder walls. This procedure should be reserved for patients with severe coagulopathy, thrombocytopenia, an anatomically inaccessible location, or those with a gallbladder wall thickness of ≤7 mm.

The potential limitations of this study were the small number of patients, the analysis was performed at a single tertiary-care center, the absence of patients with severe acute cholecystitis, and the lack of a control group to undergo PTGBD or PTGBA. Moreover, because of the small sample size of the study, we could not perform validation of the diagnostic tree in the independent data set, and the control for confounding factors by multivariate analysis was insufficient. The validity of the effects of the predictive factors and the diagnostic tree was therefore not satisfied.

In conclusion, ENGBD was effective in resolving acute cholecystitis. However, it was technically challenging and had a limited success rate. Further studies are necessary to better identify patients who would benefit the most from this procedure.

CONFLICTS OF INTEREST

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

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