Is it necessary to insert a nasobiliary drainage tube routinely after endoscopic clearance of the common bile duct in patients with choledocholithiasis-induced cholangitis? A prospective, randomized trial

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Background: Little is known about whether a routinely inserted endoscopic nasobiliary drainage (ENBD) tube improves the clinical course in patients with choledocholithiasis-induced acute cholangitis after clearance of choledocholithiasis.

Objective: The aim of this study was to investigate the need for ENBD on the clinical outcomes of patients with acute cholangitis undergoing endoscopic clearance of common bile duct (CBD) stones.

Design: Prospective, randomized study.

Setting: Tertiary referral center.

Patients: A total of 104 patients with choledocholithiasis-induced acute cholangitis who underwent primary endoscopic treatment were compared according to insertion of an ENBD tube (51 in the ENBD group and 53 in the no-ENBD group).

Intervention: Insertion of an ENBD tube after clearance of CBD stones.

Main Outcome Measurements: Recurrence of cholangitis and length of hospital stay after clearance of CBD stones.

Results: Baseline clinical characteristics were similar between both groups. There were no significant differences in the recurrence rate of cholangitis at 24 weeks (3.9% for the ENBD group vs 3.8% for the no-ENBD group at 24 weeks; $P = .99$) and length of hospital stay (7.9 days [standard error = 1.2] for the ENBD group vs 7.9 days [standard error = 0.7] for the no-ENBD group; $P = .98$). However, procedure time was longer (26.2 [SE = 1.8] minutes vs 22.7 [SE = 1.0] minutes, respectively; $P = .01$) and the discomfort score was higher (4.9 [SE = 0.4] vs 2.8 [SE = 0.3], respectively; $P = .02$) in the ENBD group than in the no-ENBD group.

Limitations: Single-center study.

Conclusions: A routinely inserted ENBD tube did not improve the clinical course, despite patients having to endure increased procedure time and discomfort, and the insertion would therefore be unnecessary. (Gastrointest Endosc 2010;71:105-10.)

Abbreviations: CBD, common bile duct; ENBD, endoscopic nasobiliary drainage; EST, endoscopic sphincterotomy; PTBD, percutaneous transhepatic biliary drainage.

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Endoscopic intervention is the treatment of choice for patients with acute cholangitis caused by common bile duct (CBD) stones, with a high success rate and a low complication rate, and endoscopic sphincterotomy (EST) with extraction of stones plays a pivotal role.[1-5] Although it is still a matter of debate, a number of endoscopists preferentially insert either an endoscopic nasobiliary drainage (ENBD) tube or a biliary stent for decompression or

removal of infected bile before or after stone extraction. Although both an ENBD tube and a biliary stent can readily be placed safely in most cases, they each have shortcomings. A patient with an ENBD tube will experience discomfort in the nostril and face and will need a bile-collecting bag. The placement of a biliary stent necessitates 1 or more duodenoscopy sessions for replacement or removal. Some studies prospectively compared the efficacy of a temporarily inserted ENBD tube and a biliary stent until the definite clearance of the CBD,[6-9] and 1 randomized study compared the results of full EST with stone extraction and those of minor EST with a biliary stent.[10] There have been, however, few studies concerning the effectiveness of the placement of an ENBD tube after clearance of the CBD. The aim of this prospective, randomized trial was to determine whether there were additional benefits in clinical outcomes of patients with acute cholangitis undergoing primary EST with CBD clearance if an ENBD tube was inserted routinely.

Capsule Summary

What is already known on this topic

- In the setting of acute cholangitis caused by common bile duct stones, some endoscopists insert either an endoscopic nasobiliary drainage (ENBD) tube or a biliary stent for decompression of infected bile.

What this study adds to our knowledge

- In104 patients with acute cholangitis and choledocholithiasis who underwent primary endoscopic treatment with or without routine insertion of an ENBD tube, no significant differences were seen in the 24-week recurrence rate of cholangitis or in the length of hospital stay.
- Not surprisingly, the procedure time was longer and the discomfort greater in the ENBD group.

METHODS

Study population

Patients who were hospitalized for choledocholithiasis-induced acute cholangitis at Dongguk University International Hospital from March 1, 2006 to September 30, 2007 were enrolled in the study. The diagnosis of acute cholangitis was made when clinical evidence of infection (fever or leukocytosis) and biliary obstruction (jaundice or hyperbilirubinemia) was present in a patient with right upper quadrant or epigastric pain. Most of the patients underwent 64-channel spiral abdominal CT with biliary protocol initially except for a few with azotemia, who underwent noncontrast CT or MRCP instead. Patients with no documented gallstones on CT or MRCP underwent US. Therapeutic ERCP was planned when a CBD stone and/or bile duct dilation was revealed on a radiologic study.

Patients who underwent EST previously or in whom percutaneous transhepatic biliary drainage (PTBD) was planned primarily because of unstable vital signs or poor cooperation were excluded from study. The patients suspected of having intrahepatic duct stone or malignant biliary obstruction on imaging studies and those who underwent a subtotal gastrectomy were excluded. Also, patients in a comorbid state with acute pancreatitis were excluded. Those in whom either PTBD or ENBD was mandatory after the initial session of ERCP because of failure of selective cannulation or remnant stones were also excluded.

Broad-spectrum intravenous antibiotics were administered to all patients as soon as the diagnosis was made. Patients were observed closely after the procedure, and those who were in a state of systemic inflammatory response syndrome at presentation were monitored in the intensive care unit. Two or more of the following diagnostic criteria for systemic inflammatory response syndrome had to be met: temperature less than 36°C or more than 38°C, heart rate greater than 90 beats per minute, respiratory rate higher than 20 breaths per minute, and white blood cell count less than 4000/mm^3 or more than 12,000/mm^3.[11]

Sampling for complete blood count and pancreatic enzymes was done 24 and 48 hours after ERCP to evaluate the occurrence of post-ERCP pancreatitis and bleeding complications. Liver function was checked daily until the values normalized. If an unexpected remnant CBD stone was suspected, CT or MRCP was performed in the no-ENBD group and a cholangiogram via an ENBD tube was obtained in the ENBD group. All patients with proven gallstones were recommended for cholecystectomy, which was performed after the patient's clinical condition and laboratory values normalized, thus allowing general anesthesia to be administered. The ENBD tube was removed after intraoperative cholangiography in a patient undergoing cholecystectomy. For a patient with no radiologically proven gallstone, the ENBD tube was withdrawn at least 48 hours after ERCP if there was no remnant stone on the cholangiogram obtained after improvement of symptoms and abnormal laboratory values. The Institutional Review Board of Dongguk University International Hospital approved this study.

Procedures

ERCP was performed within 24 hours of hospitalization with a side-viewing duodenoscope (TJF-260; Olympus Corporation, Seoul, Korea) with the patient under the appropriate sedation with meperidine and midazolam. Duodenal relaxation was obtained with scopolamine butylbromide. Continuous cardiopulmonary monitoring was used for all patients. The operator chose the device and technique for cannulation including the precut fistulotomy technique with a needle-type sphincterotome. After

selective probing of the CBD, EST was performed with a pull-type sphincterotome. The extent of EST was determined by the size of the largest stone. Stones were removed with a basket and/or a retrieval balloon with or without mechanical lithotripsy based on the operator's decision. The CBD was considered cleared when both the operating endoscopist and the attending radiologist agreed that no stone was seen on the balloon occlusion cholangiogram. In case it was decided to insert an ENBD tube, the proximal end of it was lodged at the proximal CBD.

Randomization

Patients were randomized to undergo or not undergo routine placement of either a 5F ENBD tube with 7 side holes or a right-angle bend tip with preformed duodenal loop (Nasal Biliary Drainage Sets; Wilson Cook Medical, Inc, Winston-Salem, NC). Randomization was done in equal proportions by an independent statistician using a computer-generated random numbers program. He prepared hundreds of sealed envelopes containing random numbers for allocation, which had equal odd-even proportions. An odd number allocated the patient to the ENBD group and an even number to the no-ENBD group. An assistant nurse not taking part in the evaluation of the study outcome opened the envelopes just after completion of CBD clearance and the allocations were made.

Study outcome

Primary outcome measures. The cumulative recurrence rate of cholangitis at 24 weeks and the length of hospital stay were evaluated as the primary outcome measures. Hospital stay was defined as the length of time (days) required until patients with gallstones were eligible for cholecystectomy or discharge of patients without gallstones.

Secondary outcome measures. The clinical outcomes were assessed by the following variables: procedure time, patient discomfort on day 1 after the procedure, determined by using the visual analog scale (0, no discomfort; 10, severe discomfort), the time elapsed to the normalization of total serum bilirubin and aspartate aminotransferase levels, unexpectedly detected remnant CBD stones requiring an unplanned additional session of ERCP before surgery or discharge, and the development of a complication of endoscopic intervention such as post-ERCP pancreatitis and bleeding.

Post-ERCP pancreatitis was defined as the presence of abdominal pain lasting for more than 24 hours after ERCP with a more than threefold increase in serum amylase above the upper limit of normal[12] and graded by using CT if necessary.[13] A bleeding complication was defined as the need for blood transfusion, a decrease in hemoglobin level of greater than 2 g/dL, or hematochezia, melena, or hematemesis within 24 hours after the procedure.[14]

Outpatient follow-up

All patients were advised to present at the emergency department when cholangitis-related symptoms recurred and to visit an outpatient clinic at 8 and 24 weeks after discharge for liver function tests, even if they had no symptoms. Each patient was interviewed carefully, and if there was any suspicion of a recurrence, an imaging study was performed as soon as possible.

Statistical analysis

It was assumed that 8.5% of patients would experience a recurrence within 24 weeks, and the sample size required using the Fisher exact 2-sided test to detect a statistically significant difference ($\alpha = .05$) was 136 (68 in each group) with 80% power. Statistical analysis was performed on an intent-to-treat basis. The differences between groups in categorical variables were analyzed by using the χ^2 test with the Yates correction or the Fisher exact test, as appropriate. Mean values were expressed as mean $\pm$ standard error and compared by using Student's t test. The cumulative recurrence rate of cholangitis was calculated by using the Kaplan-Meier method and compared by using the log-rank test. Data were analyzed by using SPSS 12.0 for Windows (SPSS Inc, Chicago, Ill). Differences were considered statistically significant when P values were $< .05$.

RESULTS

A total of 104 patients were randomized from March 1, 2006, to September 30, 2007 (51 to the ENBD group and 53 to the no-ENBD group). During this period, 144 patients with choledocholithiasis-induced acute cholangitis were admitted to Dongguk University International Hospital. Of these, 8 were excluded because they underwent PTBD preceding ERCP. Five patients were omitted because of previous EST, 3 because of previous gastrectomy, and 2 because of concurrent intrahepatic duct stones. Eleven patients in whom either PTBD or ENBD was needed after the initial ERCP session were also excluded. The remaining 11 eligible patients refused to enroll in the study (Table 1).

Comparison of the 2 randomized groups showed no meaningful differences in baseline demographic and clinical characteristics and laboratory and radiologic findings (Tables 2 and 3).

Primary outcome measures

There were no significant differences in variables when assessing primary outcomes between the ENBD group and the no-ENBD group.

One (2.0%) patient from the ENBD group and 2 (3.8%) from the no-ENBD group experienced recurrences of cholangitis 8 weeks after discharge. The cumulative recurrences at 24 weeks were 2 (3.9%) from the ENBD group and 2 (3.8%) from the no-ENBD group. The rates were

TABLE 1. Patient selection process

Choledocholithiasis-induced cholangitis, total no.	144
PTBD preceding ERCP, no.	8
Previous endoscopic sphincterotomy, no.	5
Previous gastrectomy, no.	3
Concurrent intrahepatic duct stone, no.	2
Incomplete CBD clearance at the first session of ERCP, no.	11
Refused enrollment in study, no.	11
Final randomization, no.	104

PTBD, Percutaneous transhepatic biliary drainage; *CBD*, common bile duct.

TABLE 2. Baseline characteristics

Characteristic	ENBD group (n = 51)	No-ENBD group (n = 53)
Mean (SE) age, y	59.3 (3.3)	59.2 (2.8)
Sex (male/female)	26/25	29/24
Previous cholecystectomy, no. (%)	6 (11.8)	7 (13.2)
Location of pain (right upper quadrant/epigastric)	27/24	27/26
Duration of pain before presentation, d (SE)	4.7 (1.0)	4.2 (1.0)

ENBD, Endoscopic nasobiliary drainage; *SE*, standard error.

TABLE 3. Baseline laboratory and radiologic findings

	ENBD group (n = 51)	No-ENBD group (n = 53)	*P* value
White blood cell count/mm^3, mean (SE)	8596.7 (904.9)	10,448.8 (1136.4)	.26
Total bilirubin, mg/dL, mean (SE)	4.3 (1.0)	4.2 (0.5)	.92
Direct bilirubin, mg/dL, mean (SE)	3.1 (0.8)	3.0 (0.4)	.98
Alkaline phosphatase, IU/L, mean (SE)	192.8 (25.9)	186.5 (16.7)	.83
Aspartate aminotransferase, IU/L, mean (SE)	166.5 (43.8)	242.1 (80.9)	.41
Presence of gallstones, no. (%)	40/45 (88.9)	39/46 (84.8)	.83

ENBD, Endoscopic nasobiliary drainage; *SE*, standard error.

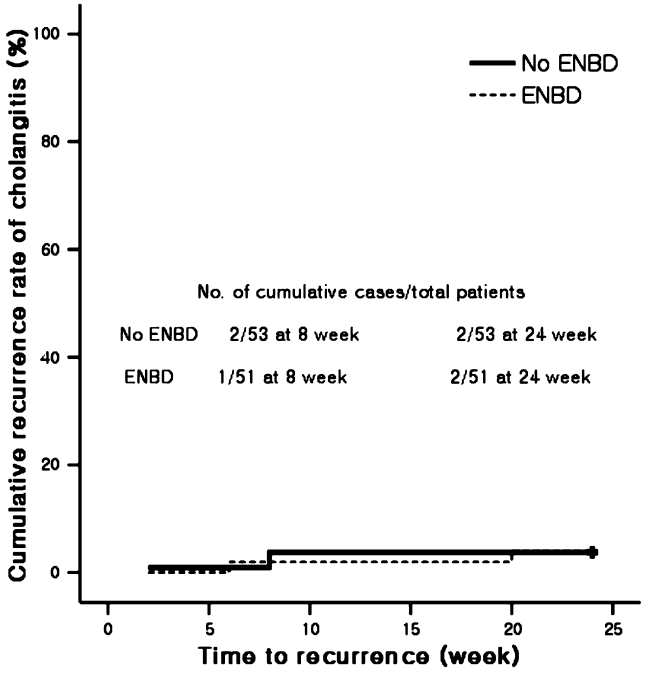

Figure 1. Estimated recurrence rates of cholangitis using the Kaplan-Meier method. They were not significantly different between the ENBD group and the no-ENBD group ($P = .96$).

not significantly different ($P = .96$) (Fig. 1). All patients experiencing a recurrence underwent successful endoscopic treatments. The length of hospital stay was also similar (7.9 ± 1.2 days for the ENBD group and 7.9 ± 0.7 days for the no-ENBD group; $P = .99$).

Secondary outcome measures

There were no significant differences in variables assessing secondary outcomes except longer total procedure time and greater patient discomfort, measured by using the visual analog scale, in the ENBD group than in the no-ENBD group ($P = .01$ and .02, respectively) (Table 4).

DISCUSSION

This randomized trial showed that the routine insertion of an ENBD tube, with prolonged procedure time and more patient discomfort, did not improve clinical outcomes in patients with acute cholangitis undergoing primary endoscopic CBD stone removal after the CBD was cleared.

Although it remains controversial, endoscopists who insert an ENBD tube after achieving CBD clearance and those who do not each have their own rationales. Cholangitis may not improve rapidly even if the stones are removed

TABLE 4. Clinical outcomes of interest

Outcome	ENBD group (n = 51)	No-ENBD group (n = 53)	*P* value
Procedure time, min (SE)	26.2 (1.8)	22.7 (1.0)	.01
Patient discomfort on day 1 VAS score 0-10, mean (SE)	4.9 (0.4)	2.8 (0.3)	.02
Normalization of total bilirubin, mean, d (SE)	3.7 (0.9)	4.1 (0.5)	.73
Normalization of aspartate aminotransferase, mean, d (SE)	6.8 (1.3)	6.9 (0.6)	.90
Time required for patients to become eligible for surgery or discharge, mean, d (SE)	7.9 (1.2)	7.9 (0.7)	.99
Unexpectedly detected remnant CBD stones before surgery or discharge, no (%)	0 (0.0)	0 (0.0)	.99
Pancreatitis after procedure	6 (11.8)	5 (9.4)	.76
Bleeding after procedure	3 (5.9)	1 (1.9)	.36
Perforation after procedure	0 (0.0)	0 (0.0)	.99

ENBD, Endoscopic nasobiliary drainage; *VAS*, visual analog scale; *SE*, standard error; *CBD*, common bile duct.

completely because edema and hemorrhage caused by endoscopic manipulations might disturb the drainage of infected bile, which might be avoided by placement of an ENBD tube. Also, bile culture is available, and a remnant stone might be readily discovered by real-time cholangiography if there is any suspicion. In contrast, there are drawbacks to the insertion of an ENBD tube. When pulling out the transnasally inserted engagement tube for an ENBD tube through the mouth with forceps, the patient expectorates a large amount of secretion by the gag reflex, and sometimes blood oozes from injury to the tongue or oral cavity. The aspiration of the secretion or blood may cause pneumonia. The extended procedure time increases radiation exposure, both to the patient and attending staff. Even after an ENBD tube is inserted successfully, patients, especially those who are confused or very old, may pull out the ENBD tube because of the discomfort caused by transnasal placement. Clogging or collapse of the tube might occur. Loss of fluid and electrolytes could be an issue. Recent British and Japanese guidelines dealt with the management of CBD stones and acute cholangitis in detail; however, they did not address the specific issue of whether a routine drainage procedure should be mandatory after endoscopic clearance of the CBD is achieved.[15-17]

Our study showed that 12 (13.2%) of 91 patients without a previous cholecystectomy had no gallstones demonstrated on radiologic studies, and we considered the removed stones to be the primary ones that developed de novo in the CBD. This observation is in accord with previous studies that reported that primary CBD stones are common in Asian countries, unlike Western countries where CBD stones are typically secondary ones that migrate from the gallbladder.[18-20] None of these patients experienced the recurrence of cholangitis or cholecystitis at 24 weeks after endoscopic treatments.

For the no-ENBD group, 2 patients experienced a recurrence of cholangitis at 8 weeks after treatment, even though it is not certain whether remnant stones caused the recurrence because neither cholangiography nor other imaging study was performed before discharge. Although 1 patient presented with mild cholangitis at the second week after discharge and recovered without problem after prompt endoscopic treatment, sepsis developed in the other patient 8 weeks after discharge. This patient had a widely dilated CBD with multiple large stones at the first presentation, and the diameter of duct was not decreased at the second presentation. Because a dilated CBD is one of the established risk factors for a recurrent CBD stone,[21,22] and there are some series that reported that placement of a biliary stent improved clinical outcomes for patients with choledocholithiasis after endoscopic treatment,[23,24] the prophylactic placement of a biliary stent could have been considered for this patient. However, because there were few studies on the use of a biliary stent for the prevention of a recurrent CBD stone and it is beyond the scope of this study, studies should be conducted in the future.

Although the fact that the number of patients did not reach the calculated sample size (68 in each group) on the final randomization might be a limitation of this study, our study is meaningful because the total number of patients during the study period was 144 and every clinical trial has inevitable patient loss because of practical problems. For our study, 11 eligible patients refused enrollment and another eligible 11 could not be randomized because clearance of CBD could not be achieved on the initial ERCP.

Post-ERCP pancreatitis developed throughout our study in a total of 11 patients. Although 10 of them experienced mild disease that improved with short-term supportive care, a 36-year-old female patient had severe

pancreatitis. At first, a single CBD stone without ductal dilation was found on CT. On ERCP, the CBD was cannulated selectively on the first probing attempt, and after EST, a small stone was removed with a basket with minimal manipulation, and no remnant stone was observed on the cholangiogram. According to the allocation, the insertion of an ENBD tube was attempted. However, recannulation was possible only after repeated attempts. Post-ERCP pancreatitis with grade E by the Balthazar CT index developed the next day. No study reported that placement of an ENBD tube per se might increase the risk of post-ERCP pancreatitis. However, because repeated cannulation attempts are an established risk factor for post-ERCP pancreatitis[25,26] and not beneficial to the clinical outcome, we think that avoiding such an unnecessary procedure would be beneficial for patients.

In conclusion, with increased procedure time and more patient discomfort, the clinical course of the patients was not improved by the routine insertion of an ENBD tube in patients with acute cholangitis undergoing primary endoscopic CBD stone removal if clearance of the CBD was achieved, and thus it would be an unnecessary procedure.

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