Original Article

The efficacy of temporary placement of nasobiliary drainage following endoscopic metal stenting to prevent post-ERCP cholangitis in patients with cholangiocarcinoma

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Abstract

Background/Aims: Although endoscopic metal biliary endoprosthesis (EMBE) is widely accepted as the most suitable drainage method for patients with unresectable malignant obstruction, uncontrolled post-procedural cholangitis is still a problem. We aimed to validate a new treatment modality to prevent post-ERCP cholangitis in patients with unresectable cholangiocarcinoma.

Patients and Methods: A total of 378 patients who were diagnosed with unresectable malignant biliary obstruction and underwent EMBE or temporary endoscopic nasobiliary drainage (ENBD) following EMBE placement, from January 2010 to July 2016, were enrolled in this retrospective study. Incidence of cholangitis, related infectious indicators, success rate of biliary drainage, and occurrence of complications were evaluated.

Results: The risk of overall cholangitis and related infectious indicators was significantly lower in EMBE plus ENBD group than that in EMBE group. The occurrence of cholangitis was 2.4% versus 11.9% ($P = 0.004$). On further analysis of subgroups, although no difference was detected in nonhilar cholangiocarcinoma subgroup, the incidence of cholangitis and related infectious indicators in hilar cholangiocarcinoma subgroup with EMBE modality were distinctly higher than that with EMBE plus ENBD modality (type I + II was 18.5% vs 0%, $P < 0.05$; type III + IV was 19.8% vs 3.8%, $P < 0.05$). No significant difference was found in successful biliary drainage rate and procedure-related complications when all subgroups were compared.

Conclusions: The temporary placement of ENBD following EMBE is a simple and effective treatment modality to prevent post-ERCP cholangitis, especially in patients with hilar cholangiocarcinoma.

Keywords: Cholangiocarcinoma, endoscopic metal biliary endoprosthesis, endoscopic nasobiliary drainage, endoscopic retrograde cholangiopancreatography, postoperative cholangitis

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INTRODUCTION

Cholangiocarcinoma, especially the hilar cholangiocarcinoma, is a common cause of malignant biliary obstruction in Southeast Asia.[1] Due to nonspecific early symptoms, the great a majority of patients are detected at an advanced stage of the disease. Therefore,

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the prognosis of cholangiocarcinoma is very poor and less than 20% of patients are suitable for curative resection.[2,3] These symptomatic patients who are not eligible for surgical resection might have to be treated with a palliative biliary drainage with endoscopic biliary drainage (EBD) or percutaneous transhepatic biliary drainage (PTBD).[4] Palliative biliary drainage helps alleviate jaundice, decompress the pressure of biliary tract, ameliorate the liver function, and prolong life expectancy.

In the last decade, with remarkable advances in endoscopic technique, the endoscopic retrograde cholangiopancreatography (ERCP) technique combined with biliary stenting is increasingly accepted as the mainstay palliative drainage appoach, which is less invasive, more comfortable, with shorter hospital stay than percutaneous drainage.[5,6] Compared with plastic stent, the self-expandable metal stent (SEMS) has been widely utilized for its advantages of longer patency and fewer reinterventions to alleviate obstructive symptoms and improve quality of life.[7,8] However, uncontrolled cholangitis after endoscopic metal biliary endoprosthesis (EMBE) is still a thorny problem, which has been shown to be a risk factor for early mortality after ERCP.[9] Hence, it remains a pivotal concern to explore new methods to prevent postoperative cholangitis.

Based on the above knowledge, we attempted to temporarily place a nasobiliary catheter with a negative pressure device following metal stenting to increase bile drainage, decompress upstream bile duct over the obstruction and decrease the incidence of post-procedure cholangitis. To the best of our knowledge, few studies involving combination of EMBE and ENBD to prevent postoperative cholangitis have been reported. In this study, we aimed to evaluate the efficacy of temporary placement of ENBD following EMBE to prevent post-ERCP cholangitis in patients with unresectable cholangiocarcinoma.

PATIENTS AND METHODS

Patients

A total of 378 consecutive patients, who were diagnosed with unresectable cholangiocarcinoma [Table 1] and who had undergone EMBE or EMBE plus ENBD treatment, were enrolled in this retrospective analysis at Shanghai General Hospital during the periods January 2010–July 2016. The participants were divided into EMBE group and EMBE plus ENBD group, depending on whether a nasobiliary drain was placed following metal stenting. The diagnosis and assessment of patients was based on an endoscopic database that combined the clinical findings, laboratory investigations, and radiological studies including computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), etc. The patients with post-ERCP pancreatitis were excluded to eliminate confounding factor of infection. The study protocol was approved by the ethical committee of the Institutional Review Board of Shanghai General Hospital.

Table 1: Criteria of inoperable cholangiocarcinoma

Patient factors
Medically unfit or otherwise unable to tolerate a major operation
Hepatic cirrhosis; portal hypertension
Local tumor-related factors
Tumor extension to secondary biliary radicles bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion
Atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicles
Unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch encasement or occlusion
Metastatic disease
Histologically proven metastases to N2 lymph nodes*
Lung, liver, or peritoneal metastases

*Peripancreatic, periduodenal, celiac, superior mesenteric, or posterior pancreaticoduodenal lymph nodes

Procedural details of ERCP

The characteristics of patients including age, gender, biochemical indicators, and hematological values were collected pre- and post-ERCP. All procedures were carried out by one of two experienced endoscopists under conscious sedation by using intravenous midazolam and pethidine. ERCP was performed in prone position with conventional therapeutic duodenoscopy (TJF-260V, Olympus, Tokyo, Japan). The common bile duct was cannulated through the duodenal papilla. If biliary cannulation was difficult, a pre-cut or endoscopic sphincterotomy (EST) was performed. The location and length of stricture and the change of intrahepatic duct could be observed carefully through slow injection of low osmolar, nonionic contrast medium called Ultravist [Figures 1 and 2]. Endoscopists placed the appropriate metal stents in the optimal location of bile duct guided by fluoroscopy [Figure 3]. In patients of EMBE plus ENBD group, the nasobiliary catheter with vacuum device was inserted and traversed the stricture when bile or contrast medium drained incompletely after insertion of metal stents [Figures 4 and 5]. Patients with hilar cholangiocarcinoma were administrated with intravenous broad-spectrum prophylactic antibiotics. The nasobiliary catheter was removed after 24 h if no cholangitis was observed.

Study outcome measurements

All patients were monitored in the hospital at least 24 h after the procedure. Related infectious indicators

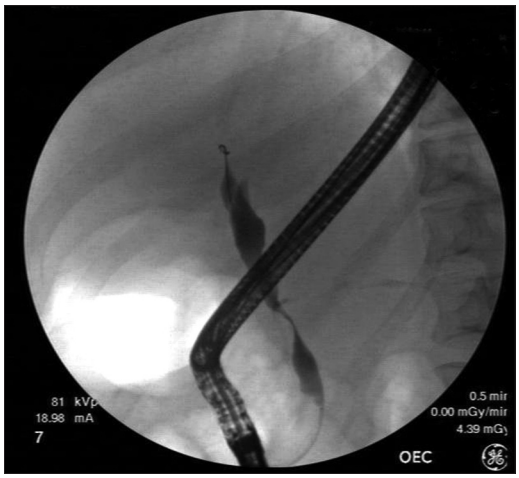

Figure 1: Cholangiography showing biliary stricture involving in the hilar region and middle of common bile duct

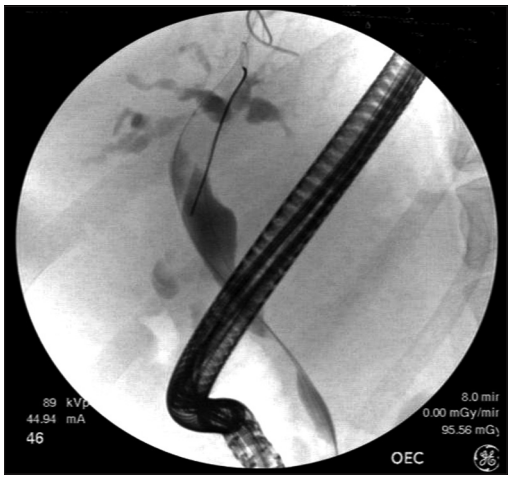

Figure 2: Dilation of intrahepatic duct was indicated with fluoroscopy after guide wire negotiated the stricture

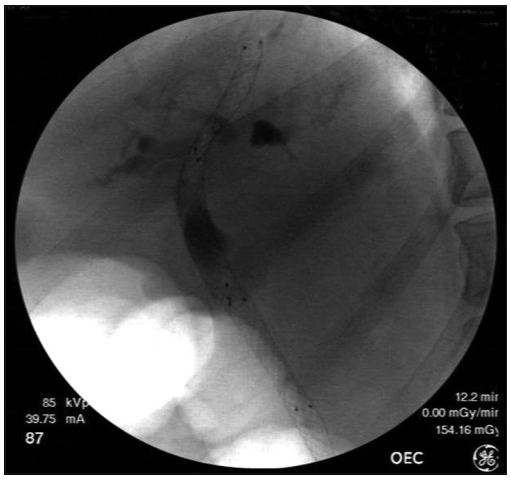

Figure 3: Two metal stents were deployed across the strictures from end to end

including white blood cell (WBC) counts, neutrophil percentage, body temperature, C-reactive protein (CRP), and biochemical examinations were evaluated to identify early post-ERCP cholangitis and other complications. Post-ERCP cholangitis was defined as abdominal pain, systemic inflammation (fever and/or shaking chills or evidence of inflammatory response consisting of abnormal WBC counts and elevated CRP levels), jaundice, elevation of bilirubin and transaminase, and imaging changes, excluding post-ERCP pancreatitis and other infectious factors.[10,11] Post-ERCP pancreatitis was diagnosed when two of the following three characteristics were noted: persistent abdominal pain for more than 24 h; elevated serum amylase or lipase, three times the upper limit of normal and imaging manifestations of acute pancreatitis.[12] Post-ERCP bleeding was indicated by the presence of hematemesis or melena, decreased serum hemoglobin level of ≥2 mg/dl and the demand for blood transfusion or a hemostatic procedure.[13] Post-ERCP perforation was diagnosed when free intraperitoneal air was presented on radiography or CT scan.[14] Successful biliary drainage was defined as immediate biliary decompression, more than 30% decrease of serum total bilirubin level after implanting metallic stents or nasobiliary drainage within 2–4 weeks.[15,16]

Statistical analysis

In this study, the main endpoint assessment was the effectiveness of preventing cholangitis. To compare the variables of the two groups, the Chi-square tests or Fisher's exact tests were applied to analyze the categorical variables described in terms of counts and percentages. Two-sample *t*-tests were used to analyze continuous variables described as the mean ± standard deviation. Statistical analysis was conducted with SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The level of significance was set at a P value < 0.05.

RESULTS

Patient characteristics

As shown in Table 2, a total of 378 patients, 252 patients with EMBE and 126 patients with EMBE plus ENBD, were enrolled in this study. Among these patients, 216 patients were diagnosed with hilar cholangiocarcinoma, with 140 in EMBE group and 76 in EMBE plus ENBD group. The remaining 162 patients were diagnosed with non-hilar cholangiocarcinoma, with 112 in EMBE group and 50 in EMBE plus ENBD group. The demographic features, infectious indicators, tumor markers, and liver function tests between the two groups showed no significant difference prior to the procedure.

Outcomes of EMBE and EMBE plus ENBD groups

The comparison of the two groups indicated that incidence rate of cholangitis and related infectious indicators were

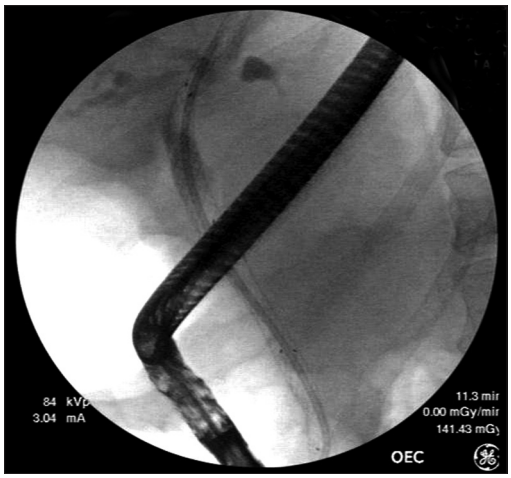

Figure 4: One nasobiliary catheter with negative pressure drainage device deployed across the portion of hilar

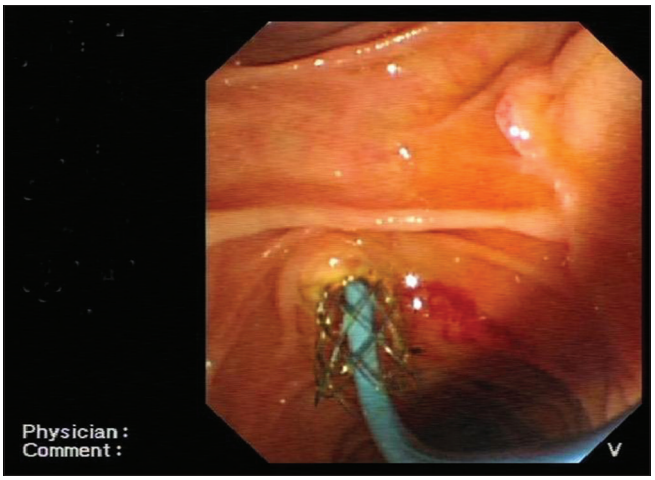

Figure 5: In view of contrast agents not completely emptied after placement of metal stents, one nasobiliary catheter with negative pressure drainage device was deployed after insertion of metal stents

significantly higher in EMBE group than that in EMBE plus ENBD group. Cholangitis occurred in 30 patients in EMBE group and in 3 patients in the EMBE plus ENBD group (11.9%, 30/252 vs 2.4%, 3/126, $P = 0.004$). The mean CRP after ERCP was 50.05 mg/L in EMBE group and 40.13 mg/L in EMBE plus ENBD group ($P = 0.001$), and WBC counts were $9.11 \pm 2.95 \times 10^9$/L in EMBE group and $8.35 \pm 3.12 \times 10^9$/L in EMBE plus ENBD group ($P = 0.023$). Successful biliary decompression was achieved in 239 of 252 patients (94.8%) in EMBE group and in 121 of 126 patients (96.0%) in EMBE plus ENBD group ($P = 0.608$). Moreover, there was no significant difference in rate of adverse events, 1.2% (3/252) in EMBE group and 0.8% (1/126) in EMBE plus ENBD group ($P = 0.652$). Three patients in EMBE group (1.2%) and one patient in EMBE plus ENBD group (0.8%) developed post-ERCP bleeding ($P = 1.000$). No perforation and immediate death occurred in any of the 378 patients. The mean hospital stay of post-ERCP demonstrated significant difference in the comparison of the two groups (3.39 days in EMBE group vs 3.08 days in EMBE plus ENBD group, $P = 0.03$), as shown in Table 3.

Outcomes of subgroup comparison

Further analysis of subgroups is indicated in Table 4. One hundred and sixty two of the 378 patients were diagnosed with non-hilar cholangiocarcinoma, with 112 patients in EMBE group and 50 patients in EMBE plus ENBD group. There were no significant differences regarding drainage success rate, incidence of cholangitis, and related infectious indicators including WBC counts, CR*P* value, and temperature. The remaining 216 patients were identified as hilar cholangiocarcinoma, among which 140 patients (54 patients with type I + II and 86 patients with III + IV) were treated with EMBE and

Table 2: Baseline demographic and clinical characteristics of the patients

Characteristics	EMBE group (*n*=252)	EMBE + ENBD group (*n*=126)	*P*
Sex (*n*, male/female)	146/106	63/63	0.143
Age (years)	72.06±9.83	73.79±10.47	0.115
Body temperature before ERCP (°C)	36.91±0.41	36.83±0.32	0.087
Value of CRP before ERCP (mg/L)	20.94±6.33	21.83±5.79	0.196
Type of obstruction			
Hilar cholangiocarcinoma	140	76	0.378
I	7	8	0.127
II	47	16	0.053
III	35	16	0.514
IV	51	36	0.117
Nonhilar cholangiocarcinoma	112	50	0.378
Tumor marker			
CA-199 (U/mL)	574.74±397.75	551.58±410.44	0.635
CA-724 (U/mL)	8.99±11.01	7.09±13.75	0.183
CA-242 (U/mL)	115.84±92.96	122.34±105.00	0.668
CA-50 (U/mL)	258.11±209.26	242.55±179.51	0.504
CEA (ng/ml)	19.22±27.46	20.50±17.96	0.612
AFP (ng/ml)	2.82±1.48	2.60±1.39	0.182
Blood test before ERCP			
WBC ($\times 10^9$/L)	7.42±2.50	7.66±3.02	0.446
NC (%)	75.08±7.76	73.73±8.85	0.148
Biochemical indicator before ERCP			
ALB (g/L)	31.43±4.70	32.47±5.46	0.058
TB (μmol/L)	272.45±88.49	283.79±78.24	0.209
ALT (U/L)	387.77±147.99	393.37±144.92	0.734

EMBE: endoscopic metal biliary endoprosthesis; ENBD: endoscopic nasobiliary drainage; ERCP: endoscopic retrograde cholangiopancreatography; CRP: C-reactive protein; CA: carbohydrate antigen; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; WBC: white blood cells; NC: neutrophil cells; ALB: albumin; TB: total bilirubin; ALT: glutamic-oxalacetic transaminase.

76 patients (24 patients with type I + II and 52 patients with type III + IV) were treated with EMBE plus ENBD. In patients with hilar cholangiocarcinoma (including type I + II and III + IV), incidence of cholangitis and

related infectious indicators differed significantly in comparison of EMBE group and EMBE plus ENBD group. Incidence of cholangitis was 18.5% (10/54) versus 0% (0/24) in type I + II ($P < 0.05$), and 19.8% (17/86) versus 3.8% (2/52) in type III + IV ($P < 0.05$). Mean CRP was 52.11 ± 13.96 mg/L versus 41.20 ± 9.57 mg/L in type I + II ($P < 0.01$), and 69.81 ± 11.75 mg/L versus 53.13 ± 9.10 mg/L in type III + IV ($P < 0.001$). Moreover, the mean hospital stay was significantly longer in EMBE group than that in EMBE plus ENBD group both in type I + II and in type III + IV (in type I + II: 3.58 days vs 3.13 days, $P = 0.033$; in type III + IV: 4.80 days vs 4.06 days, $P = 0.000$). Nevertheless, there was no significant difference in incidence of complications in all subgroups.

Table 3: Comparison between EMBE and EMBE + ENBD group

	EMBE group (*n*=252)	EMBE + ENBD group (*n*=126)	*P*
[a]Body temperature post-ERCP (°C)	37.49±0.76	37.20±0.57	0.001
[a]Value of CRP post-ERCP (mg/L)	50.05±27.60	40.13±17.09	0.001
[a]WBC counts post-ERCP (×109/L)	9.11±2.95	8.35±3.12	0.023
[a]Value of NC% post-ERCP	81.93±8.32	80.27±6.77	0.041
[b]Decreasing level of ALT post-ERCP (U/L)	168.16±49.62	186.48±45.34	0.001
[b]Decreasing level of TB post-ERCP (μmol/L)	102.66±65.95	120.78±31.15	0.000
Total incidence of cholangitis, *n* (%)	30 (11.9)	3 (2.4)	0.004
Successful biliary drainage, *n* (%)	239 (94.8)	121 (96.0)	0.608
Adverse events, *n* (%)	3 (1.2)	1 (0.8)	1.000
Bleeding	3 (1.2)	1 (0.8)	1.000
Perforation	0 (0)	0 (0)	NA
Hospital stays of post-ERCP (day)	3.39±1.46	3.08±1.22	0.030

[a]The highest value within 3 days post-ERCP. [b]The maximum value decreased within 3 days post-ERCP. EMBE: endoscopic metal biliary endoprosthesis; ENBD: endoscopic nasobiliary drainage; ERCP: endoscopic retrograde cholangiopancreatography; CRP: C-reactive protein; WBC: white blood cells; NC: neutrophil cells; TB: total bilirubin; ALT: glutamic-oxalacetic transaminase

DISCUSSION

As we currently understand, cholangiocarcinoma, which mainly presents with progressive jaundice, is one of the most common cancers throughout the world and has particularly high prevalence in certain Asian countries, such as Thailand and China.[17] Unfortunately, a majority of patients with cholangiocarcinoma are found and diagnosed at a stage when curative resection is impossible.[18] Therefore, palliative care using a minimally invasive, endoscopic procedure is the most promising option for these patients.

Multiple clinical studies indicate that EMBE, which is associated with higher successful drainage (more than 90% efficacy) and lower rate of occlusion than plastic stents, has been performed as a preferred endoscopic technique for patients with advanced malignant biliary obstruction.[4,19-25] However, it is far from optimal for patients with unresectable cholangiocarcinoma because of the intractable postoperative cholangitis, a high risk factor of mortality.

Clinically, multiple risk factors could be associated with postoperative cholangitis. For example, over injection of contrast agents would be very difficult to be drained when it gets into an obstructed intrahepatic bile duct resulting in cholangitis; lack of sterile manipulation results in bacteria being transported into the biliary tract inadvertently; operations such as endoscopic sphincterotomy, pre-cut

Table 4: Subgroup comparison between EMBE and EMBE+ENBD

	EMBE group (*n*=252)			EMBE+ENBD group (*n*=126)		
	Nonhilarc (*n*=112)	Hilar (I, II) (*n*=54)	Hilar (III, IV)(*n*=86)	Nonhilar (*n*=50)	Hilar (I, II) (*n*=24)	Hilar (III, IV) (*n*=52)
[a]Body temperature post-ERCP (°C)	37.03±0.28	37.56±0.81	38.29±0.56	36.92±0.34	37.24±0.33*	37.97±0.57*
[a]Value of CRP post-ERCP (mg/L)	31.65±30.81	52.11±13.96	69.81±11.75	29.03±17.48	41.20±9.57**	53.13±9.10***
[a]WBC counts post-ERCP (×109/L)	8.37±3.22	9.55±3.82	9.80±1.21	7.94±4.19	8.41±0.95*	8.76±2.43**
[a]Value of NC% post-ERCP	78.34±9.75	84.66±7.74	85.08±3.42	76.63±7.57	81.04±6.39*	83.67±3.48*
[b]Decreasing level of ALT post-ERCP (U/L)	190.07±41.10	167.16±52.95	139.60±43.07	200.29±38.60	185.72±27.25*	173.56±53.98***
[b]Decreasing level of TB post-ERCP (μmol/L)	133.52±73.87	100.07±60.38	63.23±24.01	143.72±26.29	119.38±24.31*	98.79±21.40***
Total incidence of cholangitis *n* (%)	3 (2.7)	10 (18.5)	17 (19.8)	1 (2.0)	0 (0)*	2 (3.8)*
Successful biliary drainage *n* (%)	109 (97.3)	51 (94.4)	79 (91.9)	49 (98.0)	23 (95.8)	49 (94.2)
Complications, *n* (%)	0 (0)	1 (1.9)	2 (2.3)	0 (0)	0 (0)	1 (1.9)
Bleeding	0	1	2	0	0	1
Perforation	0	0	0	0	0	0
Hospital stays of post-ERCP (day)	2.23±0.97	3.58±0.91	4.80±0.86	2.04±0.95	3.13±0.74*	4.06±0.73 ***

[a]The highest value within 3 days post-ERCP. [b]The maximum value decreased within 3 days post-ERCP. EMBE: endoscopic metal biliary endoprosthesis; ENBD: endoscopic nasobiliary drainage; ERCP: endoscopic retrograde cholangiopancreatography; CRP: C-reactive protein; WBC: white blood cells; NC: neutrophil cells; TB: total bilirubin; ALT: glutamic-oxalacetic transaminase. *$P<0.05$ versus EMBE group. **$P<0.01$ versus EMBE group. ***$P<0.001$ versus EMBE group

papillotomy, endoscopic papillary balloon dilation and multiple cannulation attempts induce duodenal papilla edema and reflux of intestinal contents.[26-28] In view of these risk factors, the endoscopists often perform the procedure cautiously by injecting less contrast agents, shortening operative time, and avoiding unnecessary manipulation as much as possible. However, post-ERCP cholangitis is still unavoidable. Therefore, we attempted to deploy a nasobiliary catheter with negative pressure drainage device after placement of metal stents in an effort to decrease the incidence of cholangitis.

Although it remains a matter of debate in the West regarding its discomfort for patients, a number of endoscopists prefer nasobiliary drainage for management of acute cholangitis and prevention of pancreatitis.[29-32] As a negative pressure drainage device, nasobiliary drainage has the following advantages. First, in patients with advanced hilar cholangiocarcinoma (especially Bismuth types III and IV), the obstructive sites are often located in multiple biliary branches and most of those have no communication with each other, thus making it impossible to overcome all obstructions with one or two stents. In this situation, it is difficult to distinguish between acute cholangitis in a previously drained branch due to stent occlusion, and a previously undrained biliary branch.[33] The nasobiliary tube, with multiple lateral holes as well as negative pressure aspiration device, could successfully perform the drainage of retained bile and contrast agents. Second, it enables evaluation of quality and quantity of drained bile and facilitates the collection of a bile sample for bacterial culture, which can give accurate direction for antibiotic administration. Third, negative pressure suction reduces the infectious opportunity induced by reflux of intestinal contents. In addition, it makes it convenient to perform follow up cholangiography and maintain patency by lavage. Furthermore, nasobiliary drainage can also decompress the pressure of biliary tract, keep the pancreatobiliary common channel patency, and decrease incidence of post-ERCP pancreatitis.

To the best of our knowledge, this is the first report on the efficacy of temporary placement of ENBD following EMBE to prevent post-ERCP cholangitis in patients with unresectable cholangiocarcinoma. With the understanding that long-term placement is associated with patient discomfort and complications, we chose temporary placement of ENBD for 24 h with the goal to reduce the occurrence of procedure-related cholangitis. In the present retrospective study, we found that EMBE plus ENBD modality can remarkably lower the incidence of post-ERCP cholangitis when compared with EMBE modality alone. Further analysis in subgroups of hilar cholangiocarcinoma showed that the incidence of procedure-related cholangitis, infectious indicators, values of liver function, and post-procedure hospital stays were also significantly decreased by EMBE plus ENBD treatment (especially in types III and IV). Nevertheless, these differences were not detected in patients with non-hilar cholangiocarcinoma.

In conclusion, temporary placement of ENBD following EMBE shows promise as a safe and feasible treatment modality for patients with unresectable hilar cholangiocarcinoma. Simultaneously, the study also indicated it may be unnecessary to place ENBD in patients with non-hilar cholangiocarcinoma. Nevertheless, there are several limitations to this study, including the retrospective design, lack of randomization, and the evaluation of subjects from a single center, which may limit our ability to assess the treatment efficacy objectively and exclude potential bias. Further prospective and randomized-controlled experiments should be considered.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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