Management of biliary diseases after the failure of initial needle knife precut sphincterotomy for biliary cannulation

Min-Hao Lo, Cheng-Hui Lin, Chi-Huan Wu, Yung-Kuan Tsou, Mu-Hsien Lee, Kai-Feng Sung & Nai-Jen Liu

Endoscopic retrograde cholangiopancreatography is not always successful even with needle knife precut sphincterotomy (NKPS). How to manage these patients with initial NKPS failure has not been well studied. We report the outcomes of patients who received endoscopic and non-endoscopic rescue treatment after the initial NKPS failure. During the 15 years from 2004 to 2018, 87 patients with initial NKPS failure received interval endoscopic treatment (IET group, n = 43), percutaneous transhepatic biliary drainage (PTBD group, n = 25), or bile duct surgery (BDS group, n = 19) were retrospectively studied. Compared with the PTBD group, the prevalence of choledocholithiasis was higher (69.8% vs. 16.0%, p < 0.001), and malignant bile duct stricture were lower (20.9% vs. 76.0%, p < 0.001) in the IET group. Furthermore, the IET group had a significantly longer time interval between the first and second treatment procedures (4 days vs. 2 days, p = 0.001), a lower technique success rate (79.1% vs. 100%, p = 0.021), and a shorter length of hospital stay (7 days vs. 18 days, p < 0.001). Compared to the BDS group, the only significant finding was that the patients in the IET group were older. Although not statistically significant, the complication rate was lowest in the IET group (7.0%) while highest in the BDS group (15.8%). Complications in the IET group were also mild, as compared with the other two groups. In conclusion, IET should be considered after initial failed NKPS for deep biliary cannulation before contemplating more invasive treatment such as BDS. PTBD may be the alternative therapy for patients with malignant biliary obstruction.

Patients and methods

Definition of difficult biliary cannulation. Bile duct cannulation methods in our department included cannulation using a cannula and/or a sphincterotome, with or without guidewire assistance. After the cannula/sphincterotome methods failed to achieve deep bile duct cannulation, if the pancreatic duct was cannulated, whether to perform double guidewire method or cannulation after the insertion of a pancreatic duct stent...
were combined as percutaneous transhepatic biliary drainage group (PTBD group, n = 25), and patients who in the ward. For statistical analysis, patients who received interval ERCP and interval ERCP via PTE-RVs were kind of second interventional procedure was performed depending on the decision of the attending physician received percutaneous transhepatic gallbladder drainage (PTGBD), and 19 patients (21.8%) received BDS. What 12 patients (13.8%) received interval ERCP via PTE-RVs, 21 patients (24.1%) received PTCD, 4 patients (4.36%) Among these 87 patients with a second interventional procedure, 31 patients (35.6%) received interval ERCP, procedures, technical success rate, early adverse events, length of hospital stay, and 30-day mortality.

Statistical analysis. Since the aim of the study was to report the outcomes between endoscopic and non-endoscopic treatments, comparisons were made between the IET group and the PTBD group and between the IET group and the BDS group. Continuous variables were shown as median with range, and statistical analysis for continuous variables was performed with the Mann–Whitney U test. For categorical variables, the chi-square test or Fisher exact test was used for statistical analysis whenever appropriate. Logistic regression analysis was performed to identify predictors associated with the second ERCP cannulation failure in the IET group. Statistical analyses were performed using SPSS software (version 20.0; SPSS, Inc., Chicago, IL). A two-tailed p-value of < 0.05 was considered statistically significant.
Results

There were 43 (49.4%), 25 (28.7%), and 19 (21.8%) patients in the IET, PTBD, and BDS groups, respectively. The patients’ baseline characteristics are demonstrated in Table 1. Compared with the PTBD group, patients in the IET group had significantly lower serum levels of Alk-P (median, 127 U/L vs. 211 U/L, p = 0.028) and total bilirubin (median, 2.6 mg/dL vs. 9.5 mg/dL, p = 0.007). Furthermore, the periampullary diverticulum was found to

Table 1. Clinical, laboratory, and endoscopic characteristics of the patients. IET interval endoscopic treatment, PTBD percutaneous transhepatic biliary drainage, BDS bile duct surgery, AST aspartate aminotransferase, ALT alanine aminotransferase, NS not significant between the IET group and the PTBD group and between the IET group and the BDS group. *Statistical significance between the IET group and the PTBD group. # Statistical significance between the IET group and the BDS group.

| Variables                              | IET group (n = 43) | PTBD group (n = 25) | BDS group (n = 19) | p-value |
|----------------------------------------|--------------------|---------------------|--------------------|---------|
| Median age, year (range)               | 75 (31–93)*        | 72 (45–88)          | 60 (27–79)*        | 0.004*  |
| Gender (male), n (%)                   | 21 (48.8%)         | 13 (52.0%)          | 12 (63.2%)         | NS      |
| Liver biochemistry before 1st ERCP     |                    |                     |                    |         |
| AST, median (range) (U/L)              | 70 (13–371)        | 79 (20–349)         | 132 (19–437)       | NS      |
| ALT, median (range) (U/L)              | 84 (13–447)        | 108 (11–286)        | 199 (40–509)       | NS      |
| Alkaline-P, median (range) (U/L)       | 127 (36–1281)*     | 211 (59–952)*       | 152.5 (57–869)     | 0.028*  |
| Total Bilirubin, median (range) (mg/dL)| 2.6 (0.4–9.2)*     | 9.5 (0.8–16.0)*     | 5.6 (0.9–8.6)      | 0.007*  |
| Morphology of the major papilla        |                    |                     |                    |         |
| Periampullary diverticulum, n          | 18 (41.9%)*        | 2 (8.0%)*           | 4 (21.1%)          | 0.003*  |
| Surgically altered anatomy, n          | 3 (7.0%)           | 4 (16.0%)           | 2 (10.5%)          | NS      |

Figure 1. Flow chart of the study. NKPS needle knife precut sphincterotomy, ERCP endoscopic retrograde cholangiography, PTBD percutaneous transhepatic biliary drainage.
be significantly more prevalent in the IET group (41.9% vs. 8.0%, \( p = 0.003 \)). Compared with the BDS group, the only significant finding was that patients in the IET group were older (median, 75 years vs. 60 years, \( p = 0.004 \)).

Table 2 lists the factors that might affect the choice of endoscopic versus non-endoscopic therapy for the second interventional procedure. IET interval endoscopic treatment, PTBD percutaneous transhepatic biliary drainage, BDS bile duct surgery, NS not significant between the IET group and the PTBD group and between the IET group and the BDS group. † Bleeding caused by precut, and hemostasis to prevent bleeding from blocking the endoscopic view. * Statistical significance between the IET group and the PTBD group. # Statistical significance between the IET group and the BDS group.

| Variables                                      | IET group (n = 43) | PTBD group (n = 25) | BDS group (n = 19) | p-value |
|-----------------------------------------------|--------------------|---------------------|--------------------|---------|
| Indications of the first ERCP                 |                    |                     |                    |         |
| Choledocholithiasis                           | 30 (69.8%)*        | 4 (16.0%)*          | 16 (84.2%)         | <0.001* |
| Malignant biliary stricture                   | 9 (20.9%)*         | 19 (76.0%)*         | 2 (10.5%)          | <0.001* |
| Distal bile duct obstruction, n               | 7 (17.8%)          | 17 (68.0%)          | 2 (100%)           |         |
| Hilar obstruction, n                          | 2 (22.2%)          | 2 (10.5%)           | 0                  |         |
| Benign biliary stricture or leak              | 4 (9.3%)           | 2 (8.0%)            | 1 (5.3%)           | NS      |
| Adverse events of the first ERCP, n           |                    |                     |                    |         |
| bleeding and hemostasis during NKPS †        | 19 (44.2%)         | 9 (36%)             | 6 (31.6%)          | NS      |
| Delayed Post-ERCP bleeding                    | 1 (2.3%)           | 0                   | 0                  | NS      |
| Pancreatitis                                  | 2 (4.7%)           | 0                   | 2 (10.5%)          | NS      |
| Inpatient department                          |                    |                     |                    |         |
| Medical department                            | 23 (53.5%)*        | 8 (32.0%)           | 2 (10.5%)*         | 0.001*  |
| Surgical department                           | 20 (46.5%)*        | 17 (68.0%)          | 17 (89.5%)*        | 0.001*  |

Table 3. Outcome comparisons between endoscopic versus non-endoscopic treatment. IET interval endoscopic treatment, PTBD percutaneous transhepatic biliary drainage, BDS bile duct surgery, NS not significant between the IET group and the PTBD group and between the IET group and the BDS group. * Statistical significance between the IET group and the PTBD group. # Statistical significance between the IET group and the BDS group.

| Variables                                      | IET group (n = 43) | PTBD group (n = 25) | BDS group (n = 19) | p-value |
|-----------------------------------------------|--------------------|---------------------|--------------------|---------|
| Days between 1st and 2nd procedures, median (range) | 4 (1–20)*          | 2 (0–36)*           | 3 (1–11)          | 0.001*  |
| Technical success, n                          | 34 (79.1%)*        | 25 (100%)*          | 18 (94.7%)         | 0.021*  |
| Early complications related to the second treatment, n | 3 (7.0%)          | 2 (8.0%)            | 3 (15.8%)          | NS      |
| Length of hospital stay after the second treatment, median (range) | 2 (2–40)*          | 18 (2–55)*          | 8 (2–37)          | <0.001* |
| 30-day mortality, any causes                  | 3 (7.0%)           | 4 (16.0%)           | 0                  | NS      |
| 30-day mortality related to the second treatment | 0                 | 0                   | 0                  | NS      |
of complications related to the second interventional procedure was 7% (3/43) in the IET group, 8% (2/25) in the PTBD group, and 15.8% (3/19) in the BDS group. Although there was no statistical difference in the rate of complications, the types of complications in each group were quite different. The types of complications in the IET group included 1 case of precut bleeding and 2 cases of biliary tract infection. In the PTBD group, there was 1 case of biliary tract infection and 1 case of acute biliary perforation with bile peritonitis. In the BDS group, there was 1 case of hemobilia, 1 case of hemoperitoneum, and 1 case of bile duct perforation. The 30-day mortality rate in IET, PTBD and BDS groups was 7% (3/43), 16% (4/25) and 0%, respectively (p = not significant). The causes of death of the 3 patients in the IET group were new onset of ischemic stroke, decompensated liver cirrhosis, and advanced hepatocellular carcinoma. Among the 4 patients in the PTBD group, the causes of death were advanced Klatskin tumor, advanced lung cancer, frequent seizure attacks, and decompensated liver cirrhosis combined with hepatocellular carcinoma. In each group, none with 30-day mortality was caused by the second interventional procedure.

Discussion
ERCP, PTBD, and BDS are alternative interventions used in the management of biliary diseases. ERCP has become the preferred treatment for most biliary diseases, however, it is not always successful even with NKPS even in high-volume medical centers. There is no consensus or guidelines on the management of these patients with initial NKPS failure due to difficult biliary cannulation. Several studies have shown that interval ERCP may be a viable treatment option after the initial NKPS failure, with a success rate of 68%–78%. Our success rate was 79.1% (34/43), which added to the evidence for the feasibility of interval ERCP. However, 12 of our 43 patients received interval ERCP via PTE-RVs. The success rate of interval ERCP with PTE-RVs was significantly higher than that of interval ERCP without PTE-RVs (12/12 or 100% vs. 22/31 or 71%, p = 0.04). To our knowledge, no study compares the results between interval ERCP with and without PTE-RVs. Besides, PTE-RV appears to be preferable to PTBD because PTE-RV allows physicians to perform transhepatic punctures using only small-caliber catheters, thereby reducing complications. Therefore, PTE-RVs can be used to achieve biliary access when the standard methods for biliary cannulation fail.

In theory, hyperemia and edema of the papilla caused by NKPS will improve over time, which may increase the success rate of the second ERCP. However, the optimal interval between the first and second ERCP has not yet been determined. Kim J. et al. reported that the success rate after one day was significantly lower than that 2–3 days later (65.7% vs. 88.2%, P = 0.027). Another study conducted by Colan-Hernandez et al. concluded that a second ERCP should be delayed by at least 4 days because the procedure within 4 days after the initial precut was the only significant factor associated with the second ERCP failure. However, we were unable to determine any factors related to the failure of the second ERCP, including the time interval.

The use of PTBD as an initial treatment for biliary diseases has declined in recent decades because PTBD is associated with adverse events accounting for 9%–13% and serious adverse events accounting for 4%–8%.

### Table 4

| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|----------------------|
|           | OR (95% CI)         | p-value              |
|           | OR (95% CI)         | p-value              |
| Age       |                     |                      |
| < 70 years| 1                  |                      |
| ≥ 70 years| 1.156 (0.241–5.530) | 0.856               |
| Sex       |                     |                      |
| Male      | 1                  |                      |
| Female    | 1.156 (0.241–5.530) | 0.856               |
| Indications of the first ERCP | |                      |
| Non-malignant| 1             |                      |
| Malignant | 1.778 (0.171–18.534)| 0.630               |
| Diverticulum |                 |                      |
| No        | 1                  |                      |
| Yes       | 1.143 (0.223–5.866) | 0.873               |
| Adverse events of the first ERCP | |                      |
| No        | 1                  |                      |
| Yes       | 2.625 (0.146–47.183)| 0.513               |
| Interval between two ERCP | |                      |
| < 4 days  | 1                  |                      |
| ≥ 4 days  | 0.419 (0.082–2.106)| 0.290               |
| Need precut on the second ERCP | |                      |
| No        | 1                  |                      |
| Yes       | 2.679 (0.545–13.157)| 0.225               |

Table 4. Univariate and multivariate analysis of factors associated with the second ERCP failure of patients in the interval endoscopic treatment group who did not undergo rendezvous procedures. ERCP endoscopic retrograde cholangiography, OR odds ratio.
Besides, PTBD reduces the patient's quality of life due to external drainage, and the drainage often needs to be replaced. Furthermore, it is difficult to carry out when the intrahepatic bile ducts (IHDs) are not dilated. Nevertheless, endoscopic biliary drainage is considered better than PTBD in patients with coagulopathy or ascites. However, as shown in this study, PTBD is still a useful rescue therapy in which initial ERCP fails, especially for resectable malignant biliary obstruction. 

In a recent US nationwide longitudinal study, ERCP has almost completely replaced the BDS to treat choledocholithiasis, which may be due to the improvement of the therapeutic capacity and safety of ERCP. However, due to lack of study, it is unclear whether patients who fail the initial ERCP will still experience this trend. No trend toward ERCP was found in the present study because the inpatient department seemed to affect the decision-making on the endoscopic or surgical treatment. Among the patients receiving BDS, 84.2% of patients had choledocholithiasis, and all were from the surgical department. In contrast, none of the patients with choledocholithiasis in the medical department received BDS. Just like the treatment of colon polyps, this is an interesting phenomenon because physician expertise is often closely related to treatment strategy. However, compared with the IET group, the BDS group had a higher incidence of procedure-related complications (15.8% vs. 7%, although not statistically significant) and more serious. As mentioned above, IET has an acceptably high success rate. Therefore, it is reasonable to provide endoscopic rather than surgical treatment for these patients with choledocholithiasis.

The major limitation of this study is its retrospective design, therefore, the patients in each group were not randomized. Most patients in the PTBD group were patients with malignant biliary obstruction (hence, dilated IHD). This selection bias might be the reason for the higher technical success rate of the PTBD group than the IET group. However, due to the low initial failure rate of NKPS in an experienced center, it was difficult to conduct prospective randomized studies. Second, endoscopic ultrasound-guided biliary drainage (EUS-BD) is increasingly used in patients who fail standard ERC. EUS-BD may be preferred over PTBD because of better clinical success, fewer post-procedure adverse events, and a lower rate of re-intervention. However, due to a lack of adequate expertise, it was not available in our institution during the study period.

In conclusion, IET has an acceptable success rate and less severe complications and should be tried after initial failed NKPS before contemplating more invasive interventions such as BDS. PTBD may be an alternative rescue therapy for patients with malignant biliary obstruction.

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Author contributions

M.H.L. designed and performed the research and wrote the paper; Y.K.T. designed the research and supervised the report; C.H.L. designed the research and contributed to the analysis; C.H.W. contributed to the data collection; M.H.L., K.F.S., and N.J.L. provided clinical advice.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Y.-K.T.

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