The Optimal Type and Management of Biliary Drainage in Patients With Obstructive Jaundice Who Undergo Pancreaticoduodenectomy

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Abstract. *Background/Aim:* The aims of this study were to clarify optimal type and management of preoperative biliary drainage (PBD) in patients with obstructive jaundice who underwent pancreaticoduodenectomy (PD). *Patients and Methods:* A total of 156 patients with obstructive jaundice who underwent PD were enrolled. We compared clinical variables and postoperative complications between patients who underwent endoscopic retrograde biliary drainage (ERBD) and those who underwent endoscopic nasobiliary drainage (ENBD). *Results:* All patients underwent PBD, with ERBD in 117 and ENBD in 39. The incidence of infectious complications and clinically relevant pancreatic fistula (CR-PF) were significantly higher in the ERBD group (39% vs. 13%, $p=0.012$ and 39% vs. 10%, $p<0.00001$, respectively). However, there was no significant difference in the postoperative complications between two groups when the duration of drainage exceeded 30 days. *Conclusion:* ERBD should not be performed in patients with obstructive jaundice prior to PD because of the increased rates of infectious complications and CR-PF following PD, and ENBD should be chosen instead. Furthermore, PD should be performed within 30 days of drainage period in patients with ENBD.

Biliary tract obstruction, which can cause substantial mortality and morbidity (1-3), is frequently encountered in patients with periampullary cancer. It has been reported that up to 70% of patients have some degree of biliary obstruction at the time of their initial diagnosis of pancreatic

cancer (4). Therefore, biliary stents are often placed in patients with obstructive jaundice preoperatively to relieve their symptoms such as pruritus and jaundice, which would improve surgical outcomes by overcoming the impaired immune response and coagulopathy associated with cholestasis (5).

However, biliary stents have been found to be a significant risk factor for bacterobilia, which can result in postoperative infectious complications after pancreaticoduodenectomy (PD) (6-10). It has also been reported that biliary infection, which might be evoked by preoperative biliary drainage (PBD), was significantly associated with clinically relevant pancreatic fistula (CR-PF) after PD (11-15). Van der Gaag performed a trial that randomized 94 patients to either early surgery without PBD or to PBD with delayed surgery. The rate of cumulative serious complications at 120 days was significantly higher in the PBD group than in the early surgery group. However, the difference was attributed to a very high complication rate associated with PBD procedures before surgery, rather than differences in the rate of postoperative complications (16). Moreover, some authors have claimed that PBD itself was not related to increased morbidity and mortality rates after PD, though positive bile cultures were associated with infectious morbidity, overall morbidity, and mortality (17).

Although its effect is still controversial, PBD is often inevitable in clinical practice because of the ongoing cholangitis, neoadjuvant therapy, *etc.* Recently, endoscopic drainage is selected first. Percutaneous transhepatic drainage is adopted only when endoscopic drainage is not possible. There are two different ways of endoscopic drainage: endoscopic retrograde biliary drainage (ERBD) and endoscopic nasobiliary drainage (ENBD). However, there is no consensus about which of the two drainage methods should be performed when PBD is inevitable. It is necessary to inform clinicians about the optimal type of biliary drainage in regard to postoperative complications and the useful management of PBD in patients with obstructive jaundice who undergo PD.

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Key Words: Pancreaticoduodenectomy, preoperative biliary drainage, type of biliary drainage.

Table I. Patient characteristics.

	ERBD (n=117)	ENBD (n=39)	p-Value
Age, median (range), years	70 (32-87)	71 (52-87)	0.217
Gender (male/female), n	75/42	17/22	0.025
Body mass index (range), kg/m ²	22 (15-33)	22 (17-28)	0.136
Pancreatic cancer, n (%)	63 (54%)	15 (38%)	0.400
Preoperative cholangitis, n (%)	53 (45%)	19 (49%)	0.711
Diameter of MPD, median (range), mm	3 (1.5-10)	4 (1.7-10)	0.327
Soft pancreatic parenchyma, n (%)	73 (62%)	26 (67%)	0.630
Total bilirubin before drainage, median (range), mg/dl	6.4 (2.9-30.5)	7.0 (4.7-27.1)	0.221
Total bilirubin at the time of surgery, median (range), mg/dl	0.9 (0.2-8.1)	1.6 (0.3-8.0)	0.0002
EST, n (%)	108 (92%)	17 (44%)	<0.0001
Stent exchange, yes, n (%)	54 (46%)	21 (54%)	0.405
Duration of drainage, median (range), days	33 (8-438)	26 (8-184)	0.091

MPD: Main pancreatic duct; EST: endoscopic sphincterotomy; ERBD: endoscopic retrograde biliary drainage; ENBD: endoscopic nasobiliary drainage.

The aims of this study were to clarify optimal type and management of PBD in patients with obstructive jaundice who underwent PD.

Patients and Methods

A total of 156 patients with obstructive jaundice who underwent PD for either benign pancreatic disease or malignant periampullary and pancreatic neoplasms in our institution from January 2005 to December 2019 were retrospectively analyzed. The study protocol was approved by the Clinical Research Ethics Committee of our hospital (approval number: 2019-147).

The method of endoscopic biliary drainage was decided by the endoscopists. The patients who underwent PBD were discharged and waited at home until their operation was possible.

Clinical variables including patients' characteristics, intraoperative biliary culture, postoperative morbidity and infectious complications, and the incidence of CR-PF were evaluated. Bile was sampled when the bile duct was divided during surgery and sent for Gram staining and culture.

Prophylactic antibiotics were administered to all patients and selected according to the susceptibility of the bacteria in preoperative bile cultures. In patients with negative preoperative bile cultures, a first-generation cephalosporin (cefazolin sodium hydrate) was administered.

Postoperative morbidity and mortality were defined as complications or deaths occurring within 30 days after operation or during the hospital stay. Infectious complications included postoperative pneumonia, urinary tract infection, and wound infection, bacteremia, intra-abdominal abscess. All complications were defined according to the criteria proposed by Clavien and Dindo (18). Pancreatic fistula and delayed gastric emptying were defined according to the definitions of the International Study Group on Pancreatic Fistula.

Continuous data are expressed as means±standard deviation (SD) and were compared using the Mann-Whitney *U*-test. Categorical data were assessed using the chi-squared test. Statistical analysis was carried out using JMP software (version 9.0; SAS Institute, Inc., Cary, NC, USA).

Results

A total of 156 patients (male, n=92; female, n=64) were enrolled in this study. All patients underwent PBD, with endoscopic retrograde biliary drainage (ERBD) in 117 and endoscopic nasobiliary drainage (ENBD) in 39.

There were no significant differences in age, body mass index, diameter of the main pancreatic duct, serum total bilirubin level before drainage, or the ratio of patients with pancreatic cancer, preoperative cholangitis, soft pancreatic parenchyma, and stent exchange between the ERBD group and the ENBD group. However, the ERBD group had a male predominance ($p=0.025$), low total bilirubin at the time of surgery (0.9 mg/dl) ($p=0.0002$), a high rate of performing endoscopic sphincterotomy (EST) (92%) ($p<0.0001$). Duration of drainage was relatively longer in the ERBD group than in the ENBD group though the difference was not significant (Table I).

In the ERBD group, operative time was slightly longer, and the amount of blood loss seemed to be greater, moreover, the serum levels of C-reactive protein on postoperative day 1, 3 and 5 were significantly higher than those in the ENBD group. Though there was no significant difference in amylase levels in the drainage on postoperative days 1 and 3. The incidence of CR-PF after PD was significantly greater in the ERBD group than in the ENBD group (39% vs. 10%, $p<0.0001$). Furthermore, the incidence of infectious complications was significantly greater in the ERBD group than in the ENBD group (39% vs. 13%, $p=0.012$). In particular, there were significantly more patients with wound infection and intra-abdominal abscesses in the ERBD group than in the ENBD group. Total hospital stay was not significantly different between the two groups (Table II).

Table II. Operative details and postoperative morbidity.

	ERBD (n=117)	ENBD (n=39)	p-Value
Operative details			
Operative time, median (range), min	505 (319-797)	477 (275-824)	0.102
Blood loss, median (range), ml	790 (80-6,005)	610 (170-3,140)	0.146
C-reactive protein, median (range), mg/dl			
POD 1	7.4 (3.1-29)	6.7 (1.0-17.1)	0.032
POD 3	17.0 (2.2-33.8)	9.9 (1.6-26.3)	<0.0001
POD 5	10.5 (0.4-27.8)	3.9 (0.3-21.0)	<0.0001
Amylase levels of drainage fluid, median (range), U/l			
POD 1	791 (11-32,214)	268 (17-41,735)	0.984
POD 3	375 (2-19,041)	306 (5-10,014)	0.271
Type of complication			
POPF, n (%)			
Grade A	16 (14%)	10 (26%)	0.094
CR-PF	46 (39%)	4 (10%)	<0.0001
Delayed gastric emptying, n (%)	20 (17%)	3 (8%)	0.128
Infectious complication, n (%)	46 (39%)	5 (13%)	0.012
Wound infection, n (%)	30 (26%)	4 (10%)	0.032
Intra-abdominal abscess, n (%)	23 (20%)	1 (3%)	0.003
Sepsis, n (%)	6 (5%)	0 (0%)	0.06
Catheter fever, n (%)	5 (4%)	0 (0%)	0.087
Hospital stay, median (range), days	32 (14-160)	29 (17-63)	0.063

ERBD: Endoscopic retrograde biliary drainage; ENBD: endoscopic nasobiliary drainage; POPF: postoperative pancreatic fistula; POD: postoperative day; CR-PF: clinically relevant pancreatic fistula.

Univariate and multivariate analyses were performed to identify risk factors for postoperative infectious complications and CR-PF (Table III). The multivariate analysis showed that age (≥ 70) [odds ratio (OR)=3.72; $p=0.001$], the presence of preoperative cholangitis (OR=2.74; $p=0.015$) and ERBD (OR=3.99; $p=0.0008$) were independent risk factors for postoperative infectious complications. On the other hand, male sex (OR=3.43; $p=0.008$), pancreatic texture (soft) (OR=16.69; $p=0.0002$), presence of preoperative cholangitis (OR=2.64; $p=0.031$), and ERBD (OR=11.42; $p<0.0001$) were found to be independent risk factors for CR-PF. It was shown that ERBD and the presence of preoperative cholangitis were the common risk factors for postoperative infectious complications and CR-PF.

In 47 of the 109 patients with ERBD, and in 25 of the 47 patients with ENBD, the bile juice was sampled. Positive bile juice cultures were found in all patients with ERBD (100%), but only in 13 of 25 (64%) patients with ENBD. The incidence of bile juice infection was significantly higher in patients with ERBD than in patients with ENBD. *Enterococcus* and *Enterobacter* species were the most frequent bacteria in the positive cultures in both groups (Table IV).

There was a distinct difference in the duration of drainage between patients with ERBD and ENBD. Therefore, the incidence of infectious complications was investigated by the

duration of drainage (Table V). It was found that the incidence of infectious complications and CR-PF was significantly higher in patients with ERBD than in patients with ENBD when the duration of drainage was within 30 days. However, there was no significant difference between the two groups when the duration of drainage exceeded 30 days.

Discussion

Although preoperative biliary drainage (PBD) may increase infectious complications (6-10), and it is advocated that jaundiced patients who will undergo PD should not be routinely drained before surgery, PBD is often inevitable because of cholangitis, the need for preoperative diagnosis, or when there is an indication for neoadjuvant therapy in clinical practice. Therefore, it is necessary to determine the best approach to PBD in patients who have a strong indication for PBD in whom early surgery is not feasible. In this study, the incidence rates of postoperative infectious complications and CR-PF were found to be significantly higher in patients receiving ERBD than in patients receiving ENBD.

Lee *et al.* evaluated the impact of PBD and of the type of the PBD on short-term surgical outcomes using propensity score matching (19). They reported that the overall complication rate was significantly higher in patients who underwent PBD, and the incidences of postoperative wound

Table III. Univariate and multivariate analyses of risk factors for postoperative infectious complications and CR-PF.

	Infectious complications						CR-PF					
	(+)	(-)	Univariate	Multivariate			(+)	(-)	Univariate	Multivariate		
	n=51	n=105	p-Value	OR	95%CI	p-Value	n=59	n=97	p-Value	OR	95%CI	p-Value
Gender (male, %)	37 (73)	55 (52)	0.015	1.50	0.63-3.63	0.355	43 (73)	49 (51)	0.005	3.43	1.37-9.11	0.008
Age (≥70 years, %)	36 (71)	43 (41)	0.0004	3.72	1.66-8.79	0.001	35 (59)	44 (45)	0.09			
Body mass index (≥22 kg/m ² , %)	31 (61)	37 (35)	0.003	2.15	0.96-4.86	0.061	31 (53)	37 (38)	0.079			
Histology (pancreatic cancer, %)	24 (47)	63 (60)	0.127				18 (31)	69 (71)	<0.0001	1.74	0.61-4.98	0.299
Pancreatic texture (soft pancreas, %)	37 (73)	62 (59)	0.093				55 (93)	44 (45)	<0.0001	16.69	3.58-93.04	0.0002
Preoperative cholangitis (present, %)	33 (65)	39 (35)	0.001	2.74	1.22-6.32	0.015	38 (64)	34 (35)	0.0003	2.64	1.09-6.56	0.031
Diameter of MPD (<3 mm, %)	34 (67)	50 (48)	0.024	2.00	0.88-4.67	0.099	46 (78)	38 (39)	<0.0001	1.14	0.34-3.68	0.825
Operative time (≥500 min, %)	33 (65)	48 (46)	0.025	1.53	0.60-3.94	0.375	31 (53)	50 (52)	0.904			
Blood loss (≥700 ml, %)	34 (67)	47 (45)	0.009	2.04	0.79-5.46	0.140	32 (54)	49 (51)	0.652			
Type of drainage (ERBD, %)	46 (90)	71 (68)	0.001	3.99	1.41-13.28	0.008	55 (93)	62 (64)	<0.0001	11.98	3.86-46.76	<0.0001

CR-PF: Clinically relevant pancreatic fistula; POPF: postoperative pancreatic fistula; OR: odds ratio; CI: confidence interval; ERBD: endoscopic retrograde biliary drainage; MPD: main pancreatic duct.

infections and postoperative pancreatic fistula (POPF) were significantly higher in patients who underwent endoscopic drainage than in those who underwent transhepatic biliary drainage (PTBD). They concluded that PBD, especially endoscopic drainage, should not be routinely performed in patients with periampullary cancer. Although PTBD was not investigated in the present study, considering that ENBD provides the same external drainage as PTBD, these results supported the finding that ENBD is superior to ERBD regarding postoperative complications. Fujii *et al.* also reported ERBD caused postoperative complications, including POPF, and infectious postoperative complications were more frequent than ENBD (20). One serious problem of PBD is infectious complications. Internal drainage quite often leads to infection of the biliary tract (21), although it allows normal bile flow and maintains an intestinal barrier from the perspective of intestinal immunity and the prevention of bacterial translocation (22, 23). In contrast, external drainage, such as PTBD and ENBD, reduces the risk of ascending infection in comparison to internal drainage, in which the stent is placed in the duodenum. Furthermore, ascending infection easily occurs after EST, which is performed more frequently in ERBD than ENBD. Indeed, in

Table IV. Results of bile juice cultures.

	ERBD (n=47)	ENBD (n=25)	p-Value
Positive, n (%)	47 (100%)	16 (64%)	<0.0001
Bacteria			
Enterococcus	29	11	
Enterobacter	17	7	
Klebsiella	14	5	
Streptococcus	8	1	
E. coli	3	2	
Citrobacter	3	1	
Staphylococcus	2	1	
Pseudomonas	2	1	
Serratia	0	2	

ERBD: Endoscopic retrograde biliary drainage; ENBD: endoscopic nasobiliary drainage.

this study, the incidence of infection of the bile juice that was sampled during operation was significantly higher in patients with ERBD than in patients with ENBD.

Several risk factors for CR-PF have been determined, such as male sex, soft gland texture of the pancreas, non-pancreatic

Table V. Incidences of infectious complication and CR-PF by period of duration of drainage.

	≤30 days			>30 days		
	ERBD (n=49)	ENBD (n=25)	p-Value	ERBD (n=68)	ENBD (n=14)	p-Value
Infectious complication, n (%)	15 (31%)	2 (8%)	0.020	31 (46%)	3 (21%)	0.083
POPF (grade B/C), n (%)	25 (51%)	1 (4%)	<0.0001	30 (56%)	3 (21%)	0.103

CR-PF: Clinically relevant pancreatic fistula; ERBD: endoscopic retrograde biliary drainage; ENBD: endoscopic nasobiliary drainage; POPF: postoperative pancreatic fistula.

cancer, small pancreatic duct diameter, high intraoperative blood loss, tumor location, interrupted anastomosis and drain amylase level on postoperative day 1 >4,000 IU/l (24-27). Recently, in addition, it has been reported that bacterial contamination in ascitic fluid was significantly associated with the development of CR-PF (13). It is hypothesized that endogenous enteric bacteria are the main cause of bacterial contamination in ascitic fluid. Furthermore, Ohgi *et al.* suggested that the bacteria in the ascitic fluid were derived from bacterobilia and might trigger CR-PF, because the microorganisms detected in the drainage fluid usually corresponded to the microorganisms isolated from the bile of patients with positive intraoperative bile cultures (14). Kajiwara *et al.* also reported that bile juice infection on postoperative day 1 was a significant risk factor for CR-PF, and it was significantly associated with retrograde biliary drainage, although performance of biliary drainage was not a significant risk factor for CR-PF (12). Recent studies demonstrated that bacteria were detected in the bile of 75-97% of patients who underwent PBD (28-30). Scheufele *et al.* reported that a positive intraoperative bile culture was observed in almost all patients after PBD, and PBD was associated with more antibiotic-resistant bacteria in the bile, such as *Enterococcus* species (30). However, all of these authors performed PBD only by ERBD. The present study demonstrated that the incidence of bile juice infection was significantly higher in patients with ERBD than in patients with ENBD, which suggests that retrograde infection and bacterobilia occurs more frequently in patients with ERBD. Therefore, it is obvious that the incidence of postoperative CR-PF was significantly higher in patients with ERBD than in patients with ENBD in the present study, considering that bacterial infections are correlated with the onset of CR-PF.

Some authors advocated delaying surgery for up to one month after PBD to reduce postoperative morbidity (31, 32), although the appropriate duration of PBD is still controversial. Shin *et al.* compared an early surgery group (≤2 weeks) and a late surgery group (≥3 weeks) after PBD, and they found that major complications of Clavien–Dindo grade II or higher occurred more frequently in the late surgery group (33). Fujii *et al.* also recently reported that

receiver operating characteristic curve analysis for the preoperative drainage period in ERBD patients determined that the cutoff level for the onset of POPF was 29 days (20). In the present study, there was no significant difference between the patients who underwent ERBD and those who underwent ENBD when the period of PBD exceeded 30 days, although the incidences of infectious complications and CR-PF were significantly higher in patients with ERBD when the duration of drainage was within 30 days. This finding indicates that retrograde infection occurs even in patients with ENBD as well as those with ERBD when the duration of drainage becomes longer.

On multivariate analysis, it was found that ERBD and the presence of preoperative cholangitis were the common significant risk factors for postoperative infectious complications and CR-PF. These results mean that infected bile juice is at the root of these complications. In fact, intraoperative bile cultures showed that the incidence of bile juice infection was significantly higher in patients with ERBD than that in patients with ENBD, which could be explained by the easy occurrence of retrograde infection in ERBD. Therefore, it is considered that ERBD should be avoided, especially when preoperative cholangitis is present.

There are some limitations to this study, because it was retrospective and had a heterogeneous group of subjects from a single institution. First, inevitable selection bias might exist, because which type of PBD to perform was decided by the internist or surgeons. However, there were no significant differences with respect to clinical characteristics between the patients who underwent ENBD and those who underwent ERBD, except for sex, in this study. Second, the duration of drainage was not decided by clear criteria. Actually, the duration of drainage was significantly shorter in patients who underwent ENBD. Therefore, further investigation based on the period of drainage should be performed. Though this retrospective study had these limitations, it demonstrated the superiority of ENBD over ERBD with respect to the incidences of postoperative infectious complications and CR-PF.

In conclusion, ERBD was associated with higher incidence of postoperative infectious complications and CR-

PF following PD than ENBD. ERBD should not be performed because of the increased rate of infectious complications and CR-PF following PD, and ENBD should be chosen instead. Furthermore, it is recommended to perform PD within thirty days of ENBD period.

Conflicts of Interest

There are no conflicts of interest related to this study and no financial or material support.

Authors' Contributions

Study design: Satoh, Matsukawa. Acquisition of data: Shiozaki. Drafting of manuscript: Satoh, Manuscript editing: Shiozaki.

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