ORIGINAL SCIENTIFIC REPORT

Specific antibiotic prophylaxis based on bile cultures is required to prevent postoperative infectious complications in pancreatoduodenectomy patients who have undergone preoperative biliary drainage

Takeshi Sudo, MD, Yoshiaki Murakami, MD, Kenichiro Uemura, MD, Yasuo Hayashidani, MD, Yasushi Hashimoto, MD, Hiroki Ohge, MD, Taijiro Sueda, MD.

Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Short title: Bile cultures in pancreatoduodenectomy

Correspondence: Takeshi Sudo, MD.
Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Telephone number: +81-82-257-5216
Fax number: +81-82-257-5219
E-mail address: tsudo@hiroshima-u.ac.jp

ABSTRACT

Background: Preoperative biliary drainage (PBD) is associated with bacterial contamination of bile, but the effects of PBD on morbidity after pancreatoduodenectomy remain controversial. The aim of this study was to characterize bile contamination in order to develop successful specific antibiotic prophylactic strategies for pancreatoduodenectomy.

Methods: Ninety-one consecutive patients who underwent pancreatoduodenectomy for periampullary tumor were prospectively evaluated. Prophylactic antibiotics were selected based on preoperative bile cultures. Bile cultures and postoperative complications were compared in 46 patients who underwent PBD (drainage group) versus 45 patients who did not (non-drainage group).

Results: The incidence of positive bile cultures was higher in the drainage group: 78% versus 36% in the non-drainage group ($P<0.001$). In the drainage group, positive bile cultures were frequently polymicrobial (61%) and demonstrated resistance to several antibiotics including cefazolin (83%), cefmetazole (72%), and cefpirome (64%). Overall (30% and 22%) and infectious (13% and 11%) morbidity did not differ significantly between the drainage and non-drainage groups, respectively.

Conclusions: PBD had a notable influence on bile microbial contamination, including a higher rate of antibiotic resistance. Therefore, specific antibiotic prophylaxis based on bile culture is required for preventing infectious complications in pancreatoduodenectomy patients who undergo PBD.

Pancreatoduodenectomy is currently performed in high-volume centers, with a very low mortality fewer than 5 %.[1-3] However, despite advances in patient selection, surgical technique, and postoperative care, most large series still report postoperative morbidity rates in the range from 30 to 50 %.[1, 2, 4, 5] Some of the potential risk factors associated with increased morbidity after pancreatoduodenectomy in jaundiced patients have been described.[1, 6, 7] However, neither randomized controlled trials nor retrospective comparative studies have provided sufficient evidence to support the use of preoperative biliary drainage (PBD) for improvement in postoperative course after pancreatoduodenectomy.[8, 9] The influence of PBD, including endoscopic or percutaneous transhepatic biliary drainage or stenting, in the jaundiced patients on outcome after pancreatoduodenectomy remains controversial.[6, 7, 10-12] Higher rates of infectious complications after pancreatoduodenectomy in patients who have undergone PBD have been reported.[6, 7, 12] This increased rate of infectious complications has been suggested to be caused at least in part by bile microbial contamination.[13, 14] Bile microbial contamination has also been reported as a major risk factor for postoperative sepsis after cholecystectomy[15] and hepatectomy.[16, 17] Recently, it has been reported that performance of intraoperative bile culture during pancreatoduodenectomy influences postoperative infectious morbidity and mortality.[13, 14] The purpose of the present prospective study is to characterize the pathogens in bile cultures obtained during pancreatoduodenectomy and their

susceptibility to antibiotics, as well as to determine the impact of specific antibiotic prophylaxis based on the bile cultures on postoperative course.

PATIENTS AND METHODS

Patient Population

This study included 91 consecutive patients who underwent pancreatoduodenectomy at the Department of Surgery, Hiroshima University Hospital between January 2000 and December 2006, from whom preoperative or intraoperative bile cultures were obtained and clinical data were collected prospectively. Pathologic diagnoses of the patients were as follows: 27 pancreatic ductal adenocarcinomas, 18 ampullary carcinomas, 14 bile duct carcinomas, 19 intraductal papillary-mucinous neoplasms, 5 other malignant diseases, and 8 other benign diseases. Patients were separated into two groups: those who had undergone PBD comprised the drainage group (n=46), while those who had not undergone PBD comprised the non-drainage group (n=45). PBD was defined as creation of an artificial conduit between the biliary tract and the exterior of the body or the gastrointestinal tract, including percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), and endoscopic biliary tube-stenting. In the drainage group, preoperative PTBD was performed in 26 patients, ENBD in 8 patients, and endoscopic biliary tube-stenting in 12 patients.

Surgical Procedures

Pylorus preserving pancreatoduodenectomy (PPPD) with regional lymphadenectomy was performed in 78 patients, and conventional Whipple's resection was performed in 13 patients. Reconstruction was routinely performed with pancreaticogastrostomy, hepaticojejunostomy, and duodenojejunostomy in PPPD or gastrojejunostomy in Whipple's resection. The surgery was performed by a single team of experienced hepatobiliary-pancreatic surgeons during the study period. Antibiotic prophylaxis was routinely administrated immediately after induction of anesthesia and then thrice daily for 2-3 days postoperatively.

Bile Cultures

In patients who had previously undergone PTBD or ENBD, bile was sampled aspirating through conduits within 1 week before surgery for bacterial examination and study of susceptibility to antibiotics. In these patients, an appropriate prophylactic antibiotic was selected based on the antimicrobial susceptibility of the preoperative bile cultures. In patients who had not previously undergone PBD or had previously undergone biliary tube-stenting, bile culture was obtained at the time of pancreatoduodenectomy when the common bile duct was surgically divided. In these patients, either cefazolin or cefpirome were routinely selected as prophylactic antibiotics.

Postoperative Complications

All infectious complications were demonstrated

bacteriologically by positive cultures and requirement for antibiotic therapy, excluding pancreatic fistula and bile leakage on which occurrence was not influenced by the use of appropriate antibiotics. Pancreatic fistula was defined using one of the following criteria: amylase level in surgical drainage fluid greater than three times the serum amylase activity on or after postoperative day 3, presence of a perianastomotic fluid collection communicating to stomach or pancreatic duct radiologically, or amylase-rich (greater than three times the serum amylase level) fluid collection, whatever its location.[18] Intraabdominal abscess was defined as the need for drainage of a fluid collection with positive cultures excluding pancreatic fistula and bile leakage. Delayed gastric emptying was defined as the need for gastric decompression beyond postoperative day 10.

Statistical Analysis

Values were expressed as median (range). Statistical analysis of qualitative variables was performed using the chi-square analysis with Fisher's exact test, and quantitative variables were performed using the unpaired t-test (2-tailed). A difference was considered statistically significant when $p<0.05$.

RESULTS

Clinicopathologic characteristics of patients, antibiotic prophylaxis, and intraoperative parameters are listed in Table1.

Pancreatic ductal adenocarcinomas and bile duct carcinomas were more frequent in the drainage group, while intraductal papillary-mucinous neoplasms and other benign diseases were more frequent in the non-drainage group (P<0.001). Values for each intraoperative parameter, including operative time, intraoperative blood loss, transfusion, were significantly higher in the drainage group than those in the non-drainage group (P<0.001, P=0.006, and P=0.007, respectively)(Table 1).

A total of 52 out of 91 patients (57%) had positive bile cultures, which were obtained preoperatively or intraoperatively during pancreatoduodenectomy. The incidence of positive bile cultures was higher in the drainage group: 78% versus 36% in the non-drainage group (P<0.001). Polymicrobial infections were present at a higher incidence in positive bile cultures from the drainage group: 61% versus 31% in the non-drainage group (P=0.047). A large variety of microorganisms were identified by bile cultures obtained preoperatively or intraoperatively during pancreatoduodenectomy (Table 2). The microorganisms most commonly isolated in the drainage and non-drainage groups were: *Enterococcus* species (39% and 16%, respectively), *Klebsiella* species (26% and 9%), *Enterobacter* species (13% and 7%), and *Pseudomonas* species (9% and 7%). In the drainage group, *Stenotrophomonas maltophilia* (17%), *Citrobacter freundii* (9%), *Alcaligenes xylosoxidans* (4%), and methicillin-resistant *Staphylococcus aureus* (4%) were isolated from bile cultures, but these were not isolated in non-drainage group (Table 2).

Susceptibility of bile microorganisms to antibiotics,

expressed on a patient basis, is shown in Table 3. In the drainage group, resistance to antibiotics was frequently noted with ampicillin (83%), cefazolin (83%), cefmetazole (72%), and cefpirome (64%). Susceptibility to antibiotics, excluding those targeted against *Enterococcus* species, was observed more frequently with imipenem-cilastatin (72%), gentamicin (67%), and ciprofloxacin (69%). While, in the non-drainage group, susceptibility to antibiotics, excluding those targeted against *Enterococcus* species, was observed more frequently with cefpirome (94%), gentamicin (94%), ciprofloxacin (94%), imipenem-cilastatin (88%). Resistance to cefpirome, imipenem-cilastatin, gentamicin was more frequently noted in the drainage group than that in the non-drainage group (Table 3).

Postoperative complications are listed in Table 4. There were no 30-days postoperative deaths. The rate of overall morbidity (ie, patients with one or more complications) was 26%. The morbidity rate in the drainage group was 30%, which was not statistically different from the non-drainage group morbidity rate of 22%. Overall, 12% of patients experienced one or more infectious complications; the infectious morbidity rate in the drainage group (13%) was not statistically different from that in the non-drainage group (11%)(Table 4).

DISCUSSION

In this prospective study, PBD had a notable influence on bile microbial contamination, with a higher rate of antibiotic

resistance noted in pancreatoduodenectomy patients with periampullary tumor. We also demonstrated a low infectious morbidity rate in patients who underwent PBD and received antibiotic prophylaxis targeted to preoperative bile microbial contamination during pancreatoduodenectomy. Our findings suggest that specific antibiotic prophylaxis based on preoperative bile cultures is required for reducing the incidence of infectious complications associated with pancreatoduodenectomy in patients who undergo PBD.

The influence of PBD after pancreatoduodenectomy on immediate outcome in jaundiced patients remains controversial. It has been suggested that preoperative jaundice is a strong determining factor of postoperative complications and should be treated preoperatively.[19] The potential advantages of PBD include improved nutritional, metabolic, and immune function, as well as a possible reduction in postoperative morbidity rates.[20] However, previous studies have not provided clear evidence that PBD improves postoperative course after pancreatoduodenectomy.[8, 9] In 1999, Povoski et al[6] reported a higher rate of infectious complications after pancreatoduodenectomy in patients who underwent PBD, and suggested that this was caused at least in part by bile contamination. However, this has not been confirmed in other large retrospective comparative studies.[7, 10-12] These studies and recent meta-analyses have concluded that PBD provides no benefits and is not associated with postoperative major complications or deaths, so it should not be used routinely, but rather selectively, in patients undergoing

pancreatoduodenectomy.[8, 9]

PBD is associated with an increased incidence of intraoperative bacteria-positive bile culture in pancreatoduodenectomy patients with periampullary tumors. In this study, bile microbial contamination was notably more frequent (78%) in the drainage group than in the non-drainage group (36%). A few studies in the literature have specifically examined PBD and its effect on intraoperative bile cultures.[13, 14, 21, 22] Preoperative endoprosthesis insertion has been reported to result in bile contamination in 47% to 94% of patients.[21, 22] Cortes et al[14] reported that in 80% of patients undergoing pancreatoduodenectomy, bile infection is related to previous interventional biliary endoscopy. Two studies have reported that PBD increases the risk of developing positive intraoperative bile cultures and increases postoperative infectious morbidity and mortality following pancreatoduodenectomy.[13, 22] One of these studies reported an association between positive intraoperative bile cultures and positive infectious complications, with similar microorganism profiles. However, the authors of the study did not provide details about whether appropriate antibiotic prophylaxis was used to prevent postoperative abdominal infection in patients with positive preoperative bile cultures. The other study reported that positive cultures were related to stenting complications, and uncomplicated stenting was not associated with increased morbidity or mortality.[22] Therefore, we suggest that during pancreatoduodenectomy for patients who have undergone PBD and who are at high risk for bile contamination,

specific antibiotic prophylaxis should be evaluated.

Cultures of preoperative or intraoperative bile from PBD patients are frequently polymicrobial and resistant to antibiotics. In this study, polymicrobial bile contamination was present in 61% of patients with positive bile culture in the drainage group. The most frequent organisms were of the *Enterococcus* species, which were isolated from 39% of patients, followed by *Klebsiella* species, *Enterobacter* species, and *Pseudomonas* species. Our results are consistent that reported that *Enterococcus* species and polymicrobial infections of gram-negative bacilli commonly develop in bile cultures in patients who undergo biliary drainage.[13, 14, 17] In the drainage group, we most often found a considerable number of typically nosocomial Gram-negative bacilli with intrinsic resistance to aminopenicillins and first- and second-generation cephalosporins, such as *Stenotrophomonas maltophilia*, *Citrobacter freundii*, and *Alcaligenes xylosoxidans*, none of which were found in the non-drainage group. These findings may be explained by the impact of antibiotics previously used during endoscopic procedures and of hospitalization history prior to surgery. Thus, an appropriate selection of antibiotics during preoperative biliary procedures is important for preventing the development of multidrug-resistant microorganisms in bile cultures.

Prevention of infectious complications after pancreatoduodenectomy also depends on an adequate antibiotic prophylaxis based on bile cultures. Antibiotic prophylaxis using first- or second-generation cephalosporins is commonly

recommended in Japan during pancreatoduodenectomy.[23] According to our results concerning susceptibility of bile microorganisms to antibiotics, blanket measurement of antibiotic prophylaxis using first- or second-generation cephalosporins is not adequate for patients undergoing PBD. Prophylactic antibiotics should be selected for each individual patient undergoing PBD based on susceptibility to antibiotics of bile microorganisms sampled through the external conduit preoperatively. However, the patients who have undergone endoscopic biliary tube-stenting do not have an external conduit through which bile can not be sampled preoperatively. In those patients, our bacteriological results are useful for choosing prophylactic antibiotics. Routine antibiotic prophylaxis relying on third- or fourth-generation cephalosporins targeting gram-negative bacilli is adequate for the patients who have undergone biliary tube-stenting. In some cases, the antibiotic have need to be changed to adequate one based on susceptibility to antibiotics of intraoperative bile cultures. In contrast, routine antibiotic prophylaxis using first- or second-generation cephalosporins is adequate for patients without PBD who are at low risk for bile contamination. However, if bile contamination is evident in intraoperative bile culture, appropriate antibiotics should be administered as soon as bile culture results are available.

In our study, a low incidence of infectious complications, including surgical site infections, after pancreatoduodenectomy was demonstrated in both patients who did (13%) and did not (11%) undergo PBD, a difference that is not

statistically significant. Although it should be noted that this analysis involved only a small number of patients, these findings indicate that specific antibiotic prophylaxis based on preoperative bile cultures has the potential to reduce the incidence of infectious complications associated with pancreatoduodenectomy for patients who undergo PBD.

REFERENCES

1. Yeo CJ, Cameron JL, Sohn TA*, et al.* Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226(3):248-257; discussion 257-260.
2. Buchler MW, Friess H, Wagner M*, et al.* Pancreatic fistula after pancreatic head resection. Br J Surg 2000; 87(7):883-889.
3. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003; 237(4):509-514.
4. Tran KT, Smeenk HG, van Eijck CH*, et al.* Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg 2004; 240(5):738-745.
5. Duffas JP, Suc B, Msika S*, et al.* A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg 2005; 189(6):720-729.

6. Povoski SP, Karpeh MS, Jr., Conlon KC*, et al.* Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg 1999; 230(2):131-142.
7. Pisters PW, Hudec WA, Hess KR*, et al.* Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001; 234(1):47-55.
8. Saleh MM, Norregaard P, Jorgensen HL*, et al.* Preoperative endoscopic stent placement before pancreaticoduodenectomy: a meta-analysis of the effect on morbidity and mortality. Gastrointest Endosc 2002; 56(4):529-534.
9. Sewnath ME, Karsten TM, Prins MH*, et al.* A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg 2002; 236(1):17-27.
10. Martignoni ME, Wagner M, Krahenbuhl L*, et al.* Effect of preoperative biliary drainage on surgical outcome after pancreatoduodenectomy. Am J Surg 2001; 181(1):52-59; discussion 87.
11. Sewnath ME, Birjmohun RS, Rauws EA*, et al.* The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg 2001; 192(6):726-734.
12. Hodul P, Creech S, Pickleman J*, et al.* The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. Am J Surg

2003; 186(5):420-425.

13. Povoski SP, Karpeh MS, Jr., Conlon KC, *et al.* Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg 1999; 3(5):496-505.
14. Cortes A, Sauvanet A, Bert F, *et al.* Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. J Am Coll Surg 2006; 202(1):93-99.
15. Wells GR, Taylor EW, Lindsay G, *et al.* Relationship between bile colonization, high-risk factors and postoperative sepsis in patients undergoing biliary tract operations while receiving a prophylactic antibiotic. West of Scotland Surgical Infection Study Group. Br J Surg 1989; 76(4):374-377.
16. Fan ST, Lai EC, Wong J. Hepatic resection for hepatolithiasis. Arch Surg 1993; 128(9):1070-1074.
17. Shigeta H, Nagino M, Kamiya J, *et al.* Bacteremia after hepatectomy: an analysis of a single-center, 10-year experience with 407 patients. Langenbecks Arch Surg 2002; 387(3-4):117-124.
18. Bassi C, Dervenis C, Butturini G, *et al.* Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138(1):8-13.
19. Dixon JM, Armstrong CP, Duffy SW, *et al.* Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. Gut 1983;

24(9):845-852.

20. Kimmings AN, van Deventer SJ, Obertop H*, et al.* Endotoxin, cytokines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage. Gut 2000; 46(5):725-731.
21. Karsten TM, Allema JH, Reinders M*, et al.* Preoperative biliary drainage, colonisation of bile and postoperative complications in patients with tumours of the pancreatic head: a retrospective analysis of 241 consecutive patients. Eur J Surg 1996; 162(11):881-888.
22. Jagannath P, Dhir V, Shrikhande S*, et al.* Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. Br J Surg 2005; 92(3):356-361.
23. Ueno T, Yamamoto K, Kawaoka T*, et al.* Current antibiotic prophylaxis in pancreatoduodenectomy in Japan. J Hepatobiliary Pancreat Surg 2005; 12(4):304-309.

Table 1. Patient characteristics, prophylactic use, and intraoperative parameters

	Drainage (n=46)	Non-drainage (n=45)	P value
Sex (male/female)	32/14	26/19	0.171
Age* (y)	71(43-83)	68(28-84)	0.054
Pathology			<0.001
Pancreatic ductal adenocarcinoma	20	7	
Ampullary carcinoma	8	10	
Bile duct carcinoma	14	0	
IPMN	2	17	
Other malignant disease	2	3	
Other benign disease	0	8	
Antibiotic prophylaxis			<0.001
Cefazolin	7	33	
Cefpirome	29	12	
Others	10	0	
Operative time*(min)	415 (270-650)	360 (250-500)	<0.001
Blood loss*(g)	1573 (400-8345)	940 (120-4100)	0.006
Transfusion*(U red cells)	0(0-33)	0(0-12)	0.007

* Data expressed as median (range)

IPMN, intraductal papillary-mucinous neoplasm

Table 2. Microorganisms isolated from pre- or intraoperative bile cultures in patients undergoing pancreatoduodenectomy

	Drainage (n=46)	Non-drainage (n=45)	P value
Positive bile culture	36(78)	16(36)	<0.001
Polymicrobial infection	22(61)	5(31)	0.047
Organisms			
Gram-negative bacilli			
Klebsiella sp	12(26)	4(9)	
Enterobacter sp	6(13)	3(7)	
Pseudomonas sp	4(9)	3(7)	
Stenotrophomonas maltophilia	8(17)	0	
Citrobacter freundii	4(9)	0	
Alcaligenes xylosoxidans	2(4)	0	
Miscellaneous	5(11)	2(4)	
Gram-positive cocci			
Enterococcus sp	18(39)	7(16)	
Streptococcus sp	4(9)	1(2)	
Staphylococcus sp	4(9)	1(2)	
[MRSA]	[2(4)]	[0]	

Parentheses represent percentage of isolated microorganisms
MRSA, methicillin-resistant *Staphylococcus aureus*

Table 3. Susceptibility to antibiotics of isolates from bile cultures, expressed on a patient basis

Antibiotics	Susceptible isolates (%)		P value
	Drainage (n=36)	Non-drainage (n=16)	
Ampicillin	17(28)	38(44)	NS
Cefazolin	17(31)	19(56)	NS
Cefmetazole	28(44)	19(56)	NS
Cefpirome	36(58)	56(94)	(0.009)
Imipenem-cilastatin	53(72)	81(88)	0.048
Gentamicin	44(67)	56(94)	(0.035)
Ciprofloxacin	53(69)	63(94)	NS

Parentheses represent percentage of susceptible isolates, excluding *Enterococcus* species

Table 4. Postoperative complications

	Drainage (n=46)	Non-drainage (n=45)	P value
Overall morbidity	14(30)	10(22)	0.258
Infectious morbidity	6(13)	5(11)	0.516
Wound infection	3(7)	2(4)	
Intraabdominal abscess	0	0	
Cholangitis	1(2)	1(2)	
Enteritis	0	1(2)	
Pneumonia	2(4)	0	
Septicemia	0	1(2)	
Pancreatic fistula	2(4)	1(2)	
Bile leakage	3(7)	2(4)	
Delayed gastric emptying	3(7)	1(2)	
Intraabdominal bleeding	0	1(2)	
Gastrointestinal bleeding	1(2)	0	
others	3(7)	2(4)	