

Etiology of bile infection and its association with postoperative complications following pancreatoduodenectomy

Saulius Grižas, Miglė Stakytė, Marius Kinčius¹, Giedrius Barauskas², Juozas Pundzius²
Clinic of Surgery, Kaunas University of Medicine Hospital, ¹Institute for Biomedical Research
²Department of Surgery, Kaunas University of Medicine, Lithuania

Key words: pancreatic cancer, pancreatoduodenectomy, cholangitis, post-operative complications.

Summary. Currently controversy exists whether bile infection following preoperative biliary drainage has an impact on postoperative complications and mortality rate. The objective of the study was to determine etiology of preoperative bile infection and to evaluate its influence on postoperative complications and mortality after pancreatoduodenectomy.

Methods. Data on 64 patients, undergoing pancreatoduodenectomy at Kaunas University of Medicine Hospital between 2002 and 2004 were collected prospectively. We evaluated etiology and the impact of bile infection on development of post-operative complications. Patients were divided into groups according to results of intraoperative bile culture.

Results. In 31 patients (48.4%) intraoperative bile cultures were negative, while in remaining 33 patients (51.6%) infected bile was documented. Both patient groups were homogenous according to demographic data, preoperative and intraoperative variables. Pancreaticoduodenectomy was performed in 21 patients after preoperative biliary drainage (endoscopic stenting, bilidigestive anastomosis or percutaneous bile drainage), others (n=43) had primary operation. Infected bile was found more often in patients who underwent biliary drainage ($p < 0.0001$). Among 43 patients with primary pancreaticoduodenectomy 22 patients underwent endoscopic retrograde cholangiopancreatography without stenting, while remaining 21 had no preoperative endoscopic manipulation. Infected bile was present in 9 patients after endoscopic retrograde cholangiopancreatography (40.9%) and in 4 without preoperative endoscopy (19%). Enterococcus and Escherichia coli dominated in bile cultures of patients with primary pancreaticoduodenectomy, while multiple species (3 and more microorganisms) dominated following drainage procedures. Septic postoperative complications were identified in 26.6% of cases. Infected bile did not influence both overall and septic postoperative complications. Bacteria causing abdominal cavity and wound infections matched bile cultures in 7.7% of cases only.

Conclusions. Our data show that infected bile is found more often after preoperative biliary drainage procedures. However, bile infection did not increase statistically significantly the number of postoperative septic complication.

Introduction

Pancreatoduodenectomy leads to major surgical trauma, resulting in substantial postoperative morbidity. Rate of postoperative complications ranges from 30% up to 65% (1, 2) and septic complications are responsible for approximately one third of postoperative morbidity (2, 3). It is still debated whether preoperative biliary drainage with consequent bile infection can lead to an increased rate of postoperative complications and mortality (2, 4).

The aim of present study was to determine association between bile infection and invasive preoperative investigations and its influence on morbidity and

mortality following pancreatoduodenectomy.

Patients and methods

Data on 64 patients, undergoing pancreatoduodenectomy at Kaunas University of Medicine Hospital between 2002 and 2004 were collected prospectively. All patients had benign or malignant periampullary tumors and underwent standardized pancreatoduodenectomy. Operative procedure has been described in detail by our group earlier (5, 6). Sex (male/female), age (exact age at the day of operation), bilirubinemia ($\mu\text{mol/l}$), patient's nutrition characterizing parameters (total protein and albumin serum levels), disease char-

acter (benign/malignant), patient's condition according to the American Society on Aging (ASA, class II or III) were evaluated prior to operation. Duration of surgery (minutes) and intraoperative blood loss (ml) were also assessed. Patients were divided into two groups according to intraoperative bile culture results: group I – patients with sterile bile (n=31); group II – patients with infected bile (n=33). We analyzed influence of endoscopic retrograde cholangiopancreatography (ERCP) and preoperative biliary drainage (endoscopic stenting, transcutaneous drainage, bilidigestive anastomosis) on development of bile infection. Postoperative complications were diagnosed using widely recognized clinical criteria. Pneumonia, bacteriemia, infected biliary or pancreatic fistula, abdominal cavity abscess and operative wound infections were assigned as septic complications.

Results are expressed as mean values \pm SD. Student's t test, Mann-Whitney or Fisher's exact test were used when appropriate. A probability value $p < 0.05$ was selected prior to the investigation as the criterion for significance of differences between the groups.

Results

Between January 2002 and November 2004 pancreatoduodenectomy was performed on 64 patients with chronic pancreatitis and benign or malignant periampullary tumors at the Department of Surgery, Kaunas University of Medicine Hospital. Intraoperative bile cultures were sterile in 31 (48.4%) patients (group I), whereas remaining 33 (51.6%) had infected bile (group II). There were no differences regarding demographic, preoperative, and intraoperative variables between the groups (Table 1).

Twenty one patients had preoperative biliary drainage (18 endoscopic stenting, 2 transcutaneous drain-

age and 1 bilidigestive anastomosis). The remaining 43 patients were operated on without preoperative bile drainage. Bile infection was observed more often in patients who had preoperative biliary drainage (20 of 21, 95.2% vs. 13 of 43, 30.2%; $p < 0.0001$) (Table 1). Among 43 patients without preoperative bile drainage 22 patients underwent ERCP as a diagnostic procedure without stenting meanwhile the remaining 21 patients had no preoperative endoscopic manipulation. Nine patients after ERCP (40.9%) and 4 without endoscopic manipulations (19%) developed infectious cholangitis. However, the difference between two subgroups was not significant ($p = 0.19$) (Fig.).

Enterococcus and *E. coli* dominated in bile cultures of patients without preoperative bile drainage, whereas *Klebsiella* was found alongside with earlier mentioned bacteria after preoperative bile drainage. Moreover, multiple species (3 and more different microorganisms) were commonly detected in these patients (14 out of 20 cases; 70%) (Table 2). In case of bacteriemia, intraabdominal sepsis, and wound complications microorganisms were identified. Coincidence of causative microorganisms with bile cultures was noticed in 1 case out of 13 (7.7%) only. In our patients *S. aureus* was mostly responsible for septic complications (7 out of 13) (Table 3).

Postoperative morbidity was documented in 31.3% of operated patients, whereas septic complications developed in 26.6% of cases (Table 4.). Postoperative complications and mortality were more frequent in patients with infected bile although the difference between the groups was not statistically significant (33.3% vs. 19.4%, $p = 0.26$). Moreover, different septic complications were similarly distributed in both groups (Table 4).

Table 1. Overall group characteristics according to demographic, preoperative, and intraoperative variables

Parameter	Infected bile group (n=33)	Sterile bile group (n=31)	p
Sex (M/F)	17/16	17/14	0.81
Age (year)	62.7 \pm 12.6	57.9 \pm 14.0	0.15
Bilirubinemia (μ mol/l)	61 \pm 73	56.8 \pm 76.8	0.83
Disease (benign/malignant)	10/23	9/22	1.0
Albumins (g/l)	37.4 \pm 4.7	36.8 \pm 5.8	0.67
Total protein (g/l)	69.1 \pm 64	67.2 \pm 8.5	0.32
ASA (II/III)	21/12	24/7	0.28
Blood loss (ml)	706 \pm 636	539 \pm 196	0.17
Operation length (min)	380 \pm 86	352 \pm 61	0.14
Preoperative biliary drainage, n	20	1	0.00001

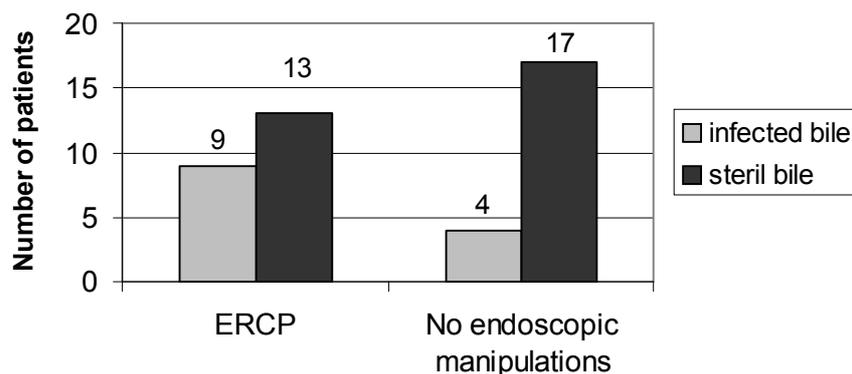


Fig. Influence of endoscopic retrograde cholangiopancreatography (ERCP) on bile infection in 43 patients without preoperative biliary drainage ($p=0.19$)

Table 2. Pathogenic microorganisms responsible for bile infection

Bacteria	Bile infection		
	no endoscopic manipulations (n=4)	ERCP (n=9)	preoperative biliary drainage (n=20)
<i>Enterococcus</i> , n	2	4	12
<i>E. coli</i> , n	2	4	7
<i>Klebsiella</i> , n	1	1	11
Polyinfection (3 or > bacteria), n	1	1	14
Others, n	1	1	2

ERCP – endoscopic retrograde cholangiopancreatography.

Table 3. Pathogenic microorganisms, responsible for development of different postoperative septic complications after pancreatoduodenectomy

Microorganism/ complication	Intra-abdominal sepsis (n=5)	Wound infection (n=3)	Bacteriemia (n=5)	Overall
<i>Staphylococcus aureus</i>	3	2	2	7
<i>Enterococcus</i> , <i>E. coli</i>	1	1	1	3
<i>Klebsiella</i>	1	–	–	1
<i>Serratia</i>	–	–	2	2
Overall	5	3	5	13

Discussion

Infected bile is a pivotal risk factor in increasing rate of septic postoperative complications such as bacteriemia, wound infection and intra-abdominal sepsis. However, it does not influence postoperative mortality and development of other complications (4, 7). It was shown recently that microorganisms found in infected bile could be detected in suppurred wounds (2, 7, 8). Furthermore, it is known that infected bile does not have direct impact on development of other infectious complications, but acting indirectly through immune system can suppress resistance of organism,

thus becoming responsible for development of pneumonia or bacteriemia. Therefore, it is important to find out the main reasons determining preoperative bile infection – preoperative biliary drainage, endoscopic stenting or other endoscopic manipulations in bile ducts.

It was shown recently that prolonged bile duct obstruction leads to impaired intestinal wall barrier function. Consequently, bacteria can colonize bile easier, thus it is not surprising that *E. coli* is the most common bacterium resulting in development of bile infection (7). It was shown also that even one preoperative

Table 4. Rate of septic complications after pancreatoduodenectomy in groups with sterile or infected bile

Patients	Group I (sterile bile) (n=31)	Group II (infected bile) (n=33)	p*
Overall morbidity, n (%)	10 (32.3%)	16 (48.5%)	0.21
Septic complication, n (%)	6 (19.4%)	11 (33.3%)	0.26
Intra-abdominal sepsis (infected fistula, abscesses), n (%)	1 (3.2%)	3 (9.1%)	0.61
Wound infection, n (%)	0 (0%)	2 (6.1%)	0.49
Pneumonia, n (%)	2 (6.4%)	3 (9.1%)	1.0
Bacteriemia, n (%)	1 (3.2%)	2 (6.1%)	1.0
Two septic complications, n (%)	2 (6.4%)	1 (3.0%)	0.61
Mortality, n (%)	0 (0%)	3 (9.1%)	0.24

*Fisher exact test.

endoscopic manipulation in bile ducts could lead to bile infection. Infectious cholangitis occurs in up to 26–55% of patients after ERCP (7, 9, 10). Subsequently, preoperative biliary drainage is the major trigger of bile infection. During endoscopic stenting procedure several bacteria usually colonize bile. Polyinfection is found in up to 70% of these patients with predominance of *Enterococcus* spp. (7, 9, 11, 12).

Similarly, our data showed that infected bile was more often observed in patients with preoperative biliary drainage and was commonly associated with polyinfection (Table 2).

To date, the influence of preoperative biliary drainage on development of postoperative septic complications is not unequivocally defined. Several clinical trails revealed significantly increased rate of septic complication after pancreatoduodenectomy following biliary drainage procedures (4, 8, 11, 13-16). Pisters *et al.* in their study with 300 patients found that preoperative endoscopic biliary duct stenting significantly enhanced the rate of postoperative wound infection. However, this manipulation influenced neither postoperative mortality rate nor development of other septic complications (4).

In contrast, Marcus *et al.* have shown that preoperative biliary drainage decreased the number of overall and infectious postoperative complications (1). Others have reported that preoperative biliary drainage and bile infection were not associated with increased rate of postoperative morbidity and mortality rates (17-21). In concordance with these results, our data revealed that bile infection after endoscopic stenting or bilidigestive anastomosis did not influence significantly the development of postoperative septic complications.

Povoski *et al.* analyzed 161 consecutive patients undergoing pancreatoduodenectomy in whom intraoperative bile cultures were obtained. Microorganisms were isolated from 58% of these cultures, with 70% of them being polymicrobial (11). In this study 29% of patients had postoperative septic complications with predominating wound infection (14%) and intra-abdominal abscess (12%). Eighty-nine percent of patients with intra-abdominal abscess and 87% of patients with wound infection had positive intraoperative bile cultures. Microorganisms in the bile were predictive of microorganisms in intra-abdominal abscess (100%) and wound infection (69%). In contrast, the coincidence of microorganisms in bile cultures and cultures from septic foci was uncommon in our study, occurring in 7.7% of cases only.

To date, there have been multiple studies in the literature analyzing preoperative biliary drainage. Although majority of these studies have produced controversial results in regard to overall and septic postoperative complications (2, 11, 14, 16, 18, 21, 22) it is recommended to avoid preoperative biliary drainage whenever resectability of periampullary tumor is established. Sufficiently powered prospective randomized studies are needed to establish unequivocally the role of preoperative biliary drainage in development of postoperative morbidity following major pancreatic surgery.

Conclusions

Based on the findings of our study we conclude that infected bile is more common following preoperative biliary drainage. However, it was associated neither with increased rate of septic complications nor mortality after pancreatoduodenectomy.

Tulžies infekuotumo priežastys ir jo įtaka pooperacinėms komplikacijoms po pankreatoduodeninių rezekcijų

Saulius Grižas, Miglė Stakytė, Marius Kinčius¹, Giedrius Barauskas², Juozas Pundzius²
Kauno medicinos universiteto klinikų Chirurgijos klinika, ¹Biomedicininų tyrimų institutas
²Kauno medicinos universiteto Chirurgijos klinika

Raktažodžiai: kasos vėžys, pankreatoduodeninė rezekcija, cholangitas, komplikacijos po operacijos.

Santrauka. Kol kas nėra visuotinai priimtinos nuomonės, kokią įtaką tulžies latakų drenavimas atliekamas prieš operaciją, sukeldamas infekcinį cholangitą, turi komplikacijoms po operacijos bei mirštamumui. Darbo tikslas. Nustatyti ikioperacinio cholangito priežastis ir įtaką pooperacinėms komplikacijoms bei mirštamumui po pankreatoduodeninių rezekcijų.

Metodai. 2002–2004 metais Kauno medicinos universiteto Chirurgijos klinikoje atlikome perspektyviają studiją, dalyvavo 64 ligoniai. Visiems buvo atliktos pankreatoduodeninės rezekcijos. Tyrėme tulžies infekuotumo priežastis ir infekcinio cholangito įtaką infekcinėms komplikacijoms po operacijos. Ligoniai suskirstyti į grupes pagal intraoperacinio tulžies pasėlio rodmenis.

Rezultatai. 31 ligoniui (48,4 proc.) pankreatoduodeninės rezekcijos metu paimtas tulžies pasėlis buvo sterilus, 33 ligoniams (51,6 proc.) – nustatyta infekuota tulžis. Abi grupės ligonių pagal ikioperacinius ar intraoperacinius duomenis buvo homogeniškos. 21 ligoniui pankreatoduodeninė rezekcija atlikta po tulžį drenuojančiosios procedūros (endoskopinis stentavimas, biliodigestyvinė jungtis arba išorinis tulžies drenažas), kitiems ligoniams (43) pankreatoduodeninė rezekcija buvo pirminė operacija. Infekuota tulžis statistiškai reikšmingai dažniau rasta ligoniams, kuriems tulžies drenažas buvo atliktas iki operacijos ($p < 0,0001$). Pirminė pankreatoduodeninė rezekcija ($n=43$), iš jų be endoskopinio stentavimo, atlikta 22 ligoniams, o 21 ligoniui jokių endoskopinių manipuliacijų tulžies latakuose nedaryta. Šių ligonių grupių bakterijos tulžyje išaugo vienodai dažnai (9 pacientams po endoskopinio stentavimo, 4 pacientams be jokių manipuliacijų, $p > 0,05$). Tulžies pasėliuose vyravo *Enterococcus* ir *Escherichia coli*, po ikioperacinio tulžies drenažo dažniausiai (70,0 proc.) buvo randama poliinfekcija (3 ir daugiau mikrobu). Pankreatoduodeninės rezekcijos komplikavosi 31,3 proc. ligonių. Sepsinių komplikacijų po operacijos nustatyta 26,6 proc. ligonių. Statistiškai reikšmingos infekcinio cholangito įtakos sepsinėms komplikacijoms po operacijos arba bendrajam komplikacijų skaičiui nenustatyta. Pilvo ertmės ir operacinės žaizdos infekcijų sukėlėjai atitiko tulžies pasėlio bakterijas tik 7,7 proc. ligonių, kitiems ligoniams sepsines komplikacijas po operacijos dažniausiai sukėlė *S. aureus*.

Išvados. Infekuota tulžis statistiškai reikšmingai dažniau nustatyta po ikioperacinio tulžies latakų drenavimo. Infekcinis cholangitas, mūsų duomenimis, statistiškai reikšmingai nedidina infekcinių komplikacijų skaičiaus po pankreatoduodeninių rezekcijų.

Adresas susirašinėti: S. Grižas, KMUK Chirurgijos klinika, Eivenių 2, 50009 Kaunas
El. paštas: saulius_grizas@yahoo.co.uk

References

1. Marcus SG, Dobryansky M, Shamamian P, Cohen H, Gouge TH et al. Endoscopic biliary drainage before pancreaticoduodenectomy for periampullary malignancies. *J Clin Gastroenterol.* 1998 Mar; 26(2):125-9.
2. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. *Ann Surg.* 1999 Aug; 230(2):131-42.
3. Halloran CM, Ghaneh P, Bosonnet L, Hartley MN, Sutton R, Neoptolemos JP. Complications of pancreatic cancer resection. *Dig Surg.* 2002; 19:138-146.
4. Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy – associate morbidity in 300 consecutive patients. *Ann Surg.* 2001 Jul; 234(1):47-55.
5. Pundzius J, Grižas S, Barauskas G. Pankreatoduodeninių rezekcijų patirtis. (Experience with pancreaticoduodenal resections). *Medicina (Kaunas)* 1999;35(10):1054-1060.
6. Barauskas G, Grižas S, Pundzius J. Virškinimo trakto vientisumo atkūrimo po pankreatoduodeninės rezekcijos metodika bei rezultatai. (Methods and results of alimentary tract reconstruction after Whipple procedure). *Medicina (Kaunas)* 2000;36(5):469-475.
7. Neve R, Biswas S, Dhir V, Mohondas KM, Kelkar R, Shukla P et al. Bile cultures and sensitivity patterns in malignant obstructive jaundice. *Indian J Gastroenterol.* 2003 Jan-Feb; 22(1):16-8.
8. Hochwald SN, Burke EC, Jarnagin WR, Fong Y, Blumgart LH. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangio-

- carcinoma. *Arch Surg.* 1999 Mar; 134(3):261-6.
9. Rerknimitr R, Fogel EL, Kalayci C, Esber E, Lehman GA. Microbiology of bile in patients with cholangitis or cholestasis with and without plastic biliary endoprosthesis. *Gastrointest Endosc.* 2002 Dec; 56(6):885-9.
 10. Nomura T, Shirai Y, Hatakeyama K. Bacteribilia and cholangitis after percutaneous transhepatic biliary drainage for malignant biliary obstruction. *Dig Dis Sci.* 1999 Mar; 44(3):542-6.
 11. Povoski SP, Karphe MS Jr, Conlon KC, Blumgart LH, Brennan MF. Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreatoduodenectomy. *J Gastrointest Surg.* 1999 Sep-Oct; 3(5):496-505.
 12. Nomura T, Shirai Y, Hatakeyama K. Enterococcal bactibilia in patients with malignant biliary obstruction. *Dig Dis Sci.* 2000 Nov; 45(11):2183-6.
 13. Hodul P, Creech S, Pickleman J, Aranha GV. The effect of preoperative biliary stenting on preoperative complications after pancreatoduodenectomy. *Am J Surg.* 2003 Nov; 186(5):420-5.
 14. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? *J Gastrointest Surg.* 2000 May-Jun; 4(3):258-67; discussion 267-8.
 15. Goyal V, Mehta JM, Jenaw RK. Does preoperative biliary stenting affect the outcome of pancreatoduodenectomy? *Indian J Gastroenterol.* 2003 Sep-Oct; 22(5):164-5.
 16. Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH, Brennan MF. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. *Arch Surg.* 1998 Feb; 133(2):149-54.
 17. Karsten TM, Allema JH, Reinders M, van Gulik TM, de Wit LT et al. Preoperative biliary drainage, colonization of bile and postoperative complications in patients with tumours of pancreatic head: a retrospective analysis of 241 consecutive patients. *Eur J Surg.* 1996 Nov; 162(11):881-8.
 18. Sewnath ME, Birjmohun RS, Rauws EA, Huibregtse K, Obertop H, Gouma DJ. The effect of preoperative biliary drainage on postoperative complications after pancreatoduodenectomy. *J Am Coll Surg.* 2001 Jun; 192(6):726-34.
 19. Martignoni ME, Wagner M, Krahenbuhl L, Redaelli CA, Friess H, Buchler MW. Effect of preoperative biliary drainage on surgical outcome a pancreatoduodenectomy. *Am J Surg.* 2001 Jan; 181(1):52-9; discussion 87.
 20. Gerke H, White R, Byrne MF, Stiffier H, Mitchell RM, Hurwitz HI et al. Complications of pancreatoduodenectomy after neoadjuvant chemoradiation in patients with and without preoperative biliary drainage. *Dig Liver Dis.* 2004 Jun; 36(6):412-8.
 21. Barauskas G, Gulbinas A, Pundzius J. Mechaninės geltos ir priešoperacinio tulžies latakų drenavimo įtaka pankreatoduodeninių rezekcijų rezultatams. (Influence of preoperative biliary drainage and obstructive jaundice on the early outcome of pancreatoduodenectomy). *Medicina (Kaunas)* 2003; 39(4):359-364.
 22. Aly EA, Johnson CD. Preoperative biliary drainage before resection in obstructive jaundice. *Dig Surg.* 2001; 18(2):84-9.

Received 31 March 2005, accepted 27 April 2005
Straipsnis gautas 2005 03 31, priimtas 2005 04 27