

Effect of Preoperative Biliary Stenting on Postoperative Complications in Patients Undergoing Pancreaticoduodenectomy

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ABSTRACT

Objective: Although preoperative biliary stenting (PBS) restores enterohepatic circulation during the preoperative period, its postoperative outcomes remain unclear. This study aimed to evaluate the effects of PBS on bacterial colonization in bile fluid and postoperative morbidity and mortality rate for pancreatic surgery.

Methods: A total of 70 patients who underwent pancreaticoduodenectomy due to periampullary tumor between January 2016 and May 2020 were analyzed retrospectively. Patients were divided into PBS and non-PBS groups. Intraoperative and postoperative outcomes were compared between the two groups.

Results: The rate of positive growth in bile culture was significantly higher in the PBS group (89.2%) compared with the non-PBS group (9.5%) ($p < 0.001$). The rates of postoperative infectious complications were found to be 85.7% and 28.5% in PBS and non-PBS groups, respectively ($p < 0.001$). In the PBS group, the rate of postoperative complications increased with the time interval between stenting and surgery ($p = 0.007$). There were no significant differences in both groups in terms of length of hospital stay and postoperative mortality ($p = 0.186$ and $p = 0.294$, respectively).

Conclusion: Biliary stenting before pancreaticoduodenectomy increases the complications such as bacterial colonization in bile fluid, postoperative wound site infection, and intra-abdominal abscess. The prolonged time between PBS and surgery increases the rate of postoperative infectious complications.

INTRODUCTION

Pancreaticoduodenectomy is considered a standard treatment for periampullary tumors. Obstructive jaundice is the most common clinical finding in periampullary tumors. Studies in mice models have shown that obstructive jaundice increases susceptibility to infection by disrupting liver T-lymphocyte and mononuclear cell functions.^[1] The biliary drainage through endoscopic or percutaneous transhepatic biliary stenting aims to restore the enterohepatic circulation in the preoperative period. The routine implementation of this common practice is controversial, and a consensus has not been reached yet on its therapeutic benefits. Several studies have shown that the biliary stent-

ing before pancreatic surgery was beneficial in preventing pathological changes due to obstructive jaundice such as itching, endotoxemia, bleeding problems, and hepatic insufficiency; those triggered by the retention of bile salts such as increased renal sodium excretion, hypovolemia, hypotension, and decreased renal perfusion.^[2,3] Biliary stenting also allows temporary stabilization for the patients who are candidates for neoadjuvant chemotherapy and gains time before elective surgery as well.^[4]

On the other hand, endoscopic and percutaneous biliary drainage eliminates the barrier function of the sphincter of Oddi and increases bacterial colonization in bile through ascending infection.^[4,5] Bile colonization has been shown to

increase the rate of postoperative infectious complications that affect surgical morbidity and mortality negatively.^[3,6,7]

In this study, we aimed to evaluate the effects of preoperative biliary stenting (PBS) on bacterial colonization in bile fluid and postoperative infectious complications, morbidity, and mortality in patients who underwent pancreaticoduodenectomy due to periampullary tumor.

MATERIALS AND METHODS

All patients who were performed pancreaticoduodenectomy due to periampullary tumor in the Hepatopancreatobiliary Clinic of the General Surgery Department at Istanbul University-Cerrahpaşa Medical Faculty between January 2016 and May 2020 were analyzed retrospectively. The study was approved by the local ethics committee (approval number: 20/04/2020-55771).

Patients with benign tumors, with malignant tumors located in the pancreas corpus and cauda, and patients considered intraoperatively inoperable were excluded from the study. The patients were divided into two groups: those who had PBS due to obstructive jaundice and those who had not (non-PBS). Patient discharge, surgery, endoscopy, and radiology reports were examined. All cases were evaluated in terms of age, gender, American Society of Anesthesiologists (ASA) physical status score, the presence of diabetes mellitus, preoperative direct bilirubin level, the length of hospital stay, postoperative infectious complications, mortality, and the leukocyte (WBC), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), and albumin levels in blood samples drawn on the fifth postoperative day. In addition, the type of microorganism growing in bile culture was recorded in patients who had been taken an intraoperative bile culture sampling. Besides, the time between stenting and surgery, method of stenting, number of restenting, and the complications related to the stent were examined.

All patients received perioperative antibiotic prophylaxis as 1 g of intravenous first-generation cephalosporin 30 min before skin incision; the second dose was added in which the operation time exceeded 4 h. Bile culture samples were taken from all patients in the PBS group and 50% (n=21) of the patients in the non-PBS group. The samples for intraoperative bile cultures were isolated just before transecting the biliary tract and sent for microbiological evaluation. To minimize the intraperitoneal contamination of the bile, the peritoneal cavity and the facial and subcutaneous planes were routinely washed with saline at the end of surgery in each case. At least one surgical drain was used while closing the abdomen.

Postoperative complications included biliary, pancreatic, duodenal, gastric, and lymphatic fistulas, abdominal abscess, postpancreatectomy hemorrhage, delayed gastric emptying, pancreatitis, urinary tract infection, pneumonia, and sepsis. Postoperative mortality was defined as death within 30 days after the day of hospital discharge and the duration of hospital stay.

Delayed gastric emptying was diagnosed according to the recommendations of the International Study Group for Pancreatic Surgery.^[8] Biliary, lymphatic, duodenal, and gastric fistulas were diagnosed based on the presence of bile or lymph fluid in surgical drains. The amylase level was examined in the sample taken from the drain fluid for the diagnosis of pancreatic anastomosis leakage in suspected cases. Abdominal collection and abscesses were confirmed by ultrasound or computed tomography. Wound infection was defined as positive culture growth from the fluid samples taken from the wound site.

Statistical analysis

Descriptive categorical data were presented as frequency and percentage; continuous variables were presented as median (interquartile range). The chi-squared test and Fisher's exact test were used, where appropriate, in the comparison of categorical data. The normal distribution of continuous variables was tested with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare nonnormally distributed data. Student's t-test was used to compare normally distributed data. A statistical significance level of $p < 0.05$ was used in all analyses. Statistical analyses were carried out with the SPSS program (version 20, IBM, Inc., Chicago, IL, USA).

RESULTS

A total of 70 patients, 28 in the PBS group and 42 in the non-PBS group, were included in the study. Of the patients in the PBS group, 22 were males and 6 were females, with a median age of 66 years. Of the patients in the non-PBS group, 22 were males and 20 were females, with a median age of 61 years. The demographic characteristics of the patients are shown in Table 1. The groups were similar in age, gender, and ASA scores ($p > 0.05$).

Table 1. Characteristics of the patients

	PBS	Non-PBS
Number of patients, n (%)	28	42
Gender (male/female)	22/6	22/20
Age, median (IQR)	66 (55.0–70.0)	61 (55–71)
ASA scores, n		
ASA 1	9	14
ASA 2	15	23
ASA 3	4	5
DM, n (%)	10 (35)	7 (16)
Primary disease		
Adenocarcinoma	27	24
Serous cystadenoma	–	7
Neuroendocrine tumor	1	6
Chronic pancreatitis	–	3
Pseudopapillary tumor	–	2

PBS: Preoperative biliary stenting; IQR: Interquartile range; ASA: American Society of Anesthesiologists; DM: Diabetes mellitus.

In the PBS group, 27 patients were stented with the endoscopic technique and 1 patient with the percutaneous transhepatic technique. Sphincterotomy was also performed in all patients who underwent endoscopic stenting. Antibiotic prophylaxis was not applied before stenting. Seven patients were found to develop cholangitis after stenting. In seven patients (25%) in the PBS group, antibiotics were applied in the preoperative period. The stent was replaced once in 6 patients and twice in 1 patient. Stent changing was not required in 21 patients. The median time between stenting and surgery was 41 days (range 11–400 days). The patient, who was operated on the 400th day after stenting, had undergone diagnostic laparotomy after the first stenting and was considered inoperable. After receiving neoadjuvant chemotherapy, cholangitis developed, and the stent was replaced in that

patient. Because of these reasons, the operation of this patient was delayed.

Intraoperative bile culture was performed for all patients in the PBS group. Positive growth was observed in 25 (89.3%) of the cultured samples. Polymicrobial bacterial growth was seen in 17 cases (60.7%). The most common microorganism was *Escherichia coli* (50%). Intraoperative bile samples for culture were isolated from 21 patients (50%) in the non-PBS group. Positive growth was observed only in 2 cases (9.5%). The rate of positive growth in bile culture was significantly higher in the PBS group compared with the non-PBS group ($p < 0.001$). The pathogenic microorganisms obtained from bile cultures are shown in Table 2.

Among postoperative complications, the rates of wound infection and intra-abdominal abscess were significantly higher in the PBS group ($p = 0.009$ and $p = 0.026$, respectively). No significant difference was found between the two groups in terms of pneumonia, sepsis, or bile leak ($p > 0.05$) (Table 3). No significant difference was found between the two groups in terms of delayed gastric emptying ($p = 0.506$). None of the patients developed postoperative hemorrhage or pancreatitis. In the PBS group, the rate of postoperative complications increased with the increasing time interval between stenting and surgery ($p = 0.007$).

The median duration of hospitalization was 18.4 days in the PBS group and 15.3 days in the non-PBS group, but the difference was not significant ($p = 0.186$). The median duration of operation was 227.5 and 216.4 min in the PBS and non-PBS groups, respectively, with a significant difference ($p = 0.032$).

Postoperative mortality was 10.7% (3 patients) in the PBS group. All the patients who died had an ASA score of 3 and polymicrobial growth in their bile cultures. Two of these patients died due to sepsis secondary to bile leak, and the other one died due to sepsis secondary to an intra-abdominal abscess. In the non-PBS group, postoperative mortality was 2.3% ($n = 1$). The cause of death was sepsis secondary to an intra-abdominal abscess. No significant difference was found between the two groups in terms of 30-day postoperative mortality ($p = 0.294$).

Table 2. Pathogenic microorganisms cultured from intraoperative bile samples

Microorganism	PBS (n)	Non-PBS (n)
<i>Escherichia coli</i>	14	1
<i>Klebsiella</i> sp.	11	0
<i>Enterococcus</i> sp.	10	0
<i>Morganella</i> sp.	5	0
<i>Pseudomonas</i> sp.	4	0
<i>Citrobacter</i> sp.	1	0
<i>Serratia</i> sp.	1	0
<i>Stenotrophomonas maltophilia</i>	1	0
<i>Staphylococcus epidermidis</i>	0	1
<i>Candida albicans</i>	1	0

PBS: Preoperative biliary stenting.

Table 3. Comparison of groups regarding duration of surgery, bile cultures, postoperative complications, length of hospital stay, and mortality

	PBS group n (%)	Non-PBS group n (%)	p
Duration of surgery (min)	227.5±27.7	216.4±24.8	0.032 ^a
Bile samples taken	28 (100.0)	21 (50.0)	<0.001 ^b
Positive bile culture	25 (89.2)	2 (9.5)	<0.001 ^b
Wound infection	9 (32.1)	3 (7.1)	0.009 ^b
Intra-abdominal abscess	9 (32.1)	4 (9.5)	0.026 ^b
Sepsis	3 (10.7)	1 (2.3)	0.294 ^b
Pneumonia	3 (10.7)	4 (9.5)	>0.05 ^b
Bile leak	2 (7.1)	0 (0.0)	0.156 ^b
Delayed gastric emptying	5 (17.8)	5 (11.9)	0.506 ^b
Duration of hospital stay (days)	18.4 (9–33)	15.3 (8–31)	0.186 ^c
Mortality	3 (10.7)	1 (2.3)	0.294 ^a

^aStudent's t-test. ^bFisher's exact test. ^cMann–Whitney U test. PBS: Preoperative biliary stenting.

Table 4. Comparison of the blood tests of patients on the fifth postoperative day

	PBS group, median (IQR)	Non-PBS group, median (IQR)	p ^a
WBC	11.9 (9.9–13.0)	9.0 (7.0–10.2)	0.002
CRP	132.5 (76.5–276.0)	80.0 (34.0–135.0)	0.044
ALP	128.5 (101.5–238.0)	102.0 (75.0–173.0)	0.026
GGT	143.0 (73.0–182.0)	63.0 (38.0–135.0)	0.003
Albumin	2.8 (2.5–3.2)	3.2 (2.9–3.4)	0.009

^aMann–Whitney U test. IQR: Interquartile range. PBS: Preoperative biliary stenting; WBC: White blood cell; CRP: C-reactive protein; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase.

There was no significant difference between the two groups in terms of preoperative serum direct bilirubin levels ($p=0.089$). Besides, no significant relationship was found between preoperative direct bilirubin levels and the frequency of postoperative complications in both PBS and non-PBS groups ($p=0.33$ and $p=0.61$, respectively). The blood levels of WBC, CRP, ALP, and GGT were significantly higher, while albumin, a negative acute phase reactant, was significantly lower in the PBS group compared with those in the non-PBS group (Table 4) in the blood samples isolated on the fifth postoperative day.

DISCUSSION

Lowering the bilirubin level is known to improve coagulation abnormalities, support the immune system, and reduce the bacterial translocation and endotoxemia.^[9] However, PBS remains a controversial subject because several recent studies have reported that PBS has negative postoperative results due to infection-related complications.^[9] Another problem is that biliary stenting has other specific complications such as pancreatitis, cholangitis, cholecystitis, and perforation.^[10] Therefore, De Pastena et al.^[11] argued that biliary stenting should not be performed routinely, but should be reserved for the patients with jaundice when the bilirubin value was above 7.5 mg/dL. European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline makes strong recommendations for preoperative biliary drainage in patients with cholangitis, severe jaundice, and delayed operation, and in those who are candidates for neoadjuvant chemotherapy.^[12] According to Tomazic and Pleskovic,^[13] biliary drainage should be done only in patients who are not candidates for resection. Among our hepatopancreatobiliary surgery team, principal indications for biliary drainage includes cholangitis and severe jaundice (the direct bilirubin level above 12 mg/dl), if early definitive surgery is not possible due to requirement of neoadjuvant chemotherapy or in case of anticipation of a several week delay in preparation for curative resection because of medical comorbidities.

Consistent with other studies in the literature, the results of the present study showed that PBS is closely associated with increased postoperative infectious complications.^[9,14–18] Biliary stenting is a significant risk factor for positive bile culture where bacterial colonization caused by microorganisms that reach the bile through ascending route from duodenum is the most likely mechanism to explain this adverse effect on postoperative results.

Some studies reported that postoperative infection-related complications were significantly more common in patients with PBS, compared with those without.^[9,14,15] Barnett and Collier^[19] reported that there was not any significant difference between these two groups in terms of infectious complications, while Lygidakis et al.^[20] reported fewer infectious complications in patients with PBS. In the present study, the rates of postoperative infectious complications were found to be 85.7% ($n=24$) and 28.5%

($n=12$) in the PBS and non-PBS groups, respectively. The rate was significantly higher in the PBS group ($p < 0.001$).

In previous studies, the most common infectious complication has been reported to be wound infections with a frequency of 6.5%–50%.^[11,15–17] A meta-analysis in current literature has shown that preoperative biliary drainage significantly increases postoperative wound infections.^[21] Bilgic et al.^[22] reported that preoperative biliary catheterization is a predictor of surgical site infection. In the present study, wound infections were the second most common complication (17%, $n=12$). We found a significantly higher rate of wound infections in patients with PBS compared with those without (32.1% and 7.1%, respectively) ($p=0.009$). Previous studies have reported the rate of intra-abdominal abscess after pancreaticoduodenectomy to be between 2% and 53% and 6% and 46% in the PBS and non-PBS groups, respectively.^[11,23–25] In line with previous studies, the rates were 30% and 8% in the present study, respectively. As in wound infection, the incidence of the intra-abdominal abscess was significantly higher in the PBS group than in the non-PBS group (32% vs 9.5%) ($p=0.026$). This positive relationship between the PBS and the rate of intra-abdominal abscess has also been reported in other case series.^[9,14,25]

There are currently no guidelines for the optimal duration of PBS. Experimental data and animal studies suggest that sufficient recovery of hepatic function requires a minimum of 4–6 weeks after preoperative biliary drainage.^[26] A prospective multicenter study reported that the delay in surgery in patients with PBS did not affect the resection rates and survival outcomes.^[27] Matsumoto et al.^[28] reported that performing surgery in the first 21 days after stenting reduces postoperative complications and affects prognosis positively. In the present study, we found that the development of postoperative complications was closely related to the time interval between stenting and operation ($p=0.007$).

In our study, we found that preoperative direct bilirubin levels did not affect postoperative complications ($p=0.33$ and $p=0.61$). Similarly, previous studies have reported that the level of preoperative bilirubin did not affect postoperative complications.^[2,9,29] Therefore, the bilirubin level should not be considered a routine indication for biliary stenting alone.^[16,29] The PBS should be implemented in selected patient groups such as those who are candidates for neoadjuvant chemotherapy and those with coagulopathy, renal failure, cholangitis, and severe malnutrition.^[9]

Delayed gastric emptying is another important complication that develops after pancreaticoduodenectomy. Previous studies reported incidences between 2% and 22% and 3% and 13% for the PBS and non-PBS groups, respectively.^[4,9,16] In our study, the incidences were 17.8% and 11.9% in the PBS and non-PBS groups, respectively, but the difference was not statistically significant ($p=0.506$).

Antibiotic prophylaxis before stenting is another topic of debate. ESGE Clinical Guideline includes the administra-

tion of antibiotic prophylaxis before biliary stenting as a weak recommendation in selected patient groups such as those with immune deficiency and anticipated to have insufficient biliary drainage.^[12] However, in a meta-analysis involving 1029 patients, Harris et al.^[30] reported that routine antibiotic prophylaxis did not reduce complications after stenting. In our study, antibiotherapy was not deemed necessary before PBS in any of the patients. As a complication, cholangitis after stenting developed in 30% of the patients. This rate was higher than those reported in the literature.^[9,10,14]

We observed that PBS increased the risk of bactobilia. The rates of positive bile culture were 89.2% and 9.5% in the PBS and non-PBS groups, respectively. The majority of positive bile cultures were reported as polymicrobial in many studies.^[4,14] Topped by *E. coli*, *Klebsiella* sp. and *Enterococcus* sp. were the most common microorganisms in bile cultures. Similarly, this set of microorganisms was frequently reported in previous studies.^[4,14] Thus, Gavazzi et al.^[4] suggested that antibiotic prophylaxis before pancreaticoduodenectomy with anti-enterococcal activity would contribute to preventing postoperative infectious complications in patients undergoing PBS. We propose that antibiotics with anti-enterococcal efficacy be administered in patients with PBS to reduce postoperative complications as a prophylaxis strategy.

Previous studies reported fungal infection in 1%–24% of bile cultures.^[31,32] In our study, *Candida albicans* growth was observed in the samples from one patient (1.7%). Some authors do not recommend prophylactic antifungal therapy.^[14] However, considering the high incidence of fungal growth in bile cultures and the absence of routine antifungal prophylaxis as opposed to antibacterial prophylaxis, the importance of *Candida* sp. should not be underestimated.

Several studies have shown that there was not any significant difference between the cases with and without biliary stenting in terms of postoperative mortality.^[9,16,23–25] The mortality rates in our study also suggest that PBS does not have a significant effect on mortality.

The limitations of our study include retrospective design, data from a single center, and the bile culture was not taken from all patients without stenting.

CONCLUSION

Biliary stenting before pancreaticoduodenectomy leads to an increase in complications such as bacterial colonization in bile fluid, postoperative wound infection, and intra-abdominal abscess. Besides, the prolonged time between biliary stenting and surgery increases the rate of postoperative complications. PBS is safe but should be used selectively because of the above-mentioned risks. We recommend preoperative biliary drainage in patients with cholangitis, severe jaundice, and delayed operation and in those who are candidates for neoadjuvant chemotherapy.

For the correct management of postoperative infectious complications, we recommend taking intraoperative bile cultures from all cases, regardless of stenting. Multicenter studies that include larger patient groups should be conducted on the subject.

Ethics Committee Approval

This study approved by the Istanbul University-Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Date: 20.04.2020, Decision No: 55771).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: S.P., K.S., M.V., O.Ş.; Design: M.V., O.Ş., O.A., B.M.; Supervision: S.P., K.S., M.V., O.Ş.; Data: B.C.T., Y.P., B.M.; Analysis: O.A., M.V., B.C.T., Y.P.; Literature search: O.A., M.V., B.C.T., Y.P., B.M.; Writing: O.A., M.V., O.Ş.; Critical revision: S.P., K.S., M.V., O.Ş.

Conflict of Interest

None declared.

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Pankreatikoduodenektomi Yapılan Hastalarda Ameliyat Öncesi Bilyer Stentlemenin Ameliyat Sonrası Komplikasyonlar Üzerine Etkisi

Amaç: Ameliyat öncesi bilyer stentleme (PBS) ameliyat öncesi dönemde enterohepatik sirkülasyonu onarmasına rağmen ameliyat sonrası sonuçları belirsiz kalmaktadır. Bu çalışma, pankreas cerrahisinde PBS'nin safra sıvısında bakteriyel kolonizasyon, ameliyat sonrası morbidite ve mortalite oranları üzerine etkilerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Periampullar tümör endikasyonu ile Ocak 2016–Mayıs 2020 arasında pankreatikoduodenektomi yapılan toplam 70 hasta geriye dönük olarak analiz edildi. Hastalar PBS ve non-PBS olmak üzere iki gruba ayrıldı. İki grup arasında ameliyat sırasında ve sonrasında sonuçlar karşılaştırıldı.

Bulgular: Safra kültüründe pozitif üreme oranı non-PBS grubuna (%9.5) kıyasla PBS grubunda (%89.2) anlamlı ölçüde daha yüksekti ($p < 0.001$). Ameliyat sonrası enfeksiyöz komplikasyonların oranı PBS ve non-PBS gruplarında sırasıyla %85.7 ve %28.5 bulundu ($p < 0.001$). PBS grubunda ameliyat sonrası komplikasyon oranı stentleme ile cerrahi arasındaki zaman aralığı ile orantılı artmaktaydı ($p = 0.007$). İki grup arasında hastanede yatış süresi ve ameliyat sonrası mortalite açısından anlamlı bir farklılık yoktu (sırasıyla; $p = 0.186$ ve $p = 0.294$).

Sonuç: Pankreatikoduodenektomi öncesi bilyer stentleme safra sıvısında bakteriyel kolonizasyon, ameliyat sonrası yara yeri enfeksiyonu ve intraabdominal apse gibi komplikasyonları arttırmaktadır. PBS ve cerrahi arası zamanın uzaması ameliyat sonrası enfeksiyöz komplikasyon oranını arttırmaktadır.

Anahtar Sözcükler: Ameliyat öncesi bilyer stentleme; ameliyat sonrası komplikasyonlar; baktibilya; pankreatikoduodenektomi.