Effects of preoperative biliary drainage methods and time to postoperative complications after biliary drainage in periampullary tumors

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Effects of preoperative biliary drainage methods and time to postoperative complications after biliary drainage in periampullary tumors

OBJECTIVE: *To compare postoperative morbidity and mortality results in patients with and without endoscopic and percutaneous transhepatic biliary drainage due to obstructive jaundice caused by a periampullary tumor and to examine the effect of intervals until surgery on postoperative morbidity and mortality in patients who underwent preoperative biliary drainage (BD).*
METHODS: *Patients were divided into 3 groups according to their BD status. Group1, no biliary drainage (NBD), Group2, Endoscopic biliary drainage (EBD), Group3, Percutaneous transhepatic biliary drainage (PBD). Patients who underwent biliary drainage before pancreaticoduodenectomy (PD) were divided into 3 intervals according to the time interval between drainage and surgery: Short interval; patients undergoing surgery in 21 days and <, Medium interval; between 22-42 days, Long interval; 43 days and >. Groups and intervals were compared in terms of postoperative morbidity and mortality.*
RESULTS: *Of the 122 patients who underwent PD, 76 (62.3%) were male, and 46 (37.7%) were female. Within these patients, 47 (38.52%) had NPD, 42 (34.42%) had EBD, and 33 (27.05%) had PBD. The rate of postoperative Grade B and C fistula was higher in the groups that underwent preoperative drainage compared to the group without preoperative drainage ($p = 0.007$).*
CONCLUSION: *It was determined that the postoperative complication rate was lower in patients who did not undergo BD compared to patients who underwent biliary drainage. Besides, the endoscopic drainage method was observed to be associated with fewer complications than the percutaneous transhepatic drainage method.*

KEY WORDS: Preoperative biliary drainage, Pancreaticoduodenectomy, Periampullary tumors, Post procedure complication, Timing

Introduction

Distal bile duct obstruction caused by periampullary tumors can cause obstructive jaundice. Hyperbilirubinemia; changes the normal physiology and increases the risk of preoperative and/or postoperative complications as well as causing multiple organ dysfunction, especially the liver, coagulation disorder, bacterial translocation, and cholangitis [1,2].

BD; has been performed for many years to reduce postoperative morbidity and mortality and improve the quality of life in icteric patients diagnosed with a periampullary tumor [3], but yet, the role of BD has been discussed for a long time.

BD can be performed via endoscopic retrograde cholangiopancreatography or percutaneous transhepatic route by interventional radiology. There is currently some dis-

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agreement about the clinical advantage and disadvantage of PBD against EBD. It has been reported that the complication rates and mortality of EBD are lower than that of PBD [4,5]. Because PBD is more invasive and is associated with a higher complication rate and a higher incidence of catheter tract metastasis [6,7].
Studies examining the effect of BD on surgical morbidity after PD have reported conflicting results [8-10]. In several recent meta-analyses, the necessity of routine BD has been questioned and it has been shown that it causes an increase in postoperative complications without any difference in mortality [11-13]. Furthermore, there are also no guidelines on the optimum timing of PD after BD [14]. The widely accepted practice is planning surgery in the earliest period if the patient does not have signs of cholangitis or if there is no need to wait for comorbid diseases or surgery [15]. It is not clear whether the time interval from BD to surgery has an effect on postoperative morbidity and mortality.
The aim of our study is to compare postoperative morbidity and mortality results in patients with and without endoscopic and percutaneous transhepatic biliary drainage due to obstructive jaundice caused by a periampullary tumor and to examine the effect of intervals until surgery on postoperative morbidity and morbidity in patients who underwent BD.

Materials and Methods

Patients and Ethics

Data of patients who underwent curative surgery with a diagnosis of clinical periampullary cancer between January 2015 and September 2020 were retrospectively evaluated from the hospital database, surgery notes, and anesthesia records. Information regarding the demographic characteristics of the patients (age, gender, ASA (American Society of Anesthesiologists) score, and concomitant diseases), preoperative biliary drainage procedure date and type of drainage (endoscopic or percutaneous), the preoperative structure of pancreatic tissue (soft or hard pancreas, pancreatic duct diameter), operation time, length of hospital stay, postoperative complications, and mortality were examined. The study was approved by the local ethics committee (non-interventional research ethics committee number 71522473/050.01.04/545).

Inclusion Criteria
Patients with good performance status (ECOG 2 and above) and ASA ≤ 3, regardless of age.

Exclusion Criteria
Patients who received neoadjuvant chemotherapy (n = 3) who underwent colon resection with PD (n = 2) and Patients who developed liver metastases during the waiting period (n = 2).

Preoperative Biliary Drainage

BD was administered via percutaneous transhepatic or endoscopic transpapillary routes to patients with a total bilirubin level of 10mg/dl or more, and/or patients with cholangitis at the time of admission, or those who were deemed eligible for neoadjuvant therapy after preoperative diagnosis.
Patients were divided into 3 groups according to their BD status. Group1, no biliary drainage (NBD), Group2, Endoscopic biliary drainage (EBD), Group3, Percutaneous transhepatic biliary drainage (PBD).
Patients who underwent biliary drainage before pancreaticoduodenectomy were divided into 3 intervals according to the time interval between drainage and surgery: Short interval; patients undergoing surgery in 21 days and <, Medium interval; between 22-42 days, Long interval; 43 days and >. Groups and intervals were compared in terms of postoperative morbidity and mortality.

Operative Data and Surgical Technique

Throughout the study period, the standard pancreaticoduodenectomy procedure was briefly as the following: In addition to the pancreatic head, uncinate process, stomach antrum, duodenum, proximal jejunum, main hepatic duct, and gall bladder were resected. Pancreatic duct diameter was measured from the pancreatic stump with a ruler. For gastrointestinal reconstruction, improved Child's technique referring to end-to-side duct-to-mucosa pancreatico-enteric anastomosis (retrocolic), end-to-side hepaticojejunostomy (retrocolic), and gastrojejunal anastomosis was used by experienced surgeons. An internal stent was placed in the pancreatic duct in all patients, and a highly easy-to-manage Wirsung-jejunostomy was preferred. Two suction drains (Jackson Pratt) were placed in the anterior and posterior of the hepaticojejunostomy and pancreaticojejunostomy in all patients. Antibiotic prophylaxis was performed with 2 grams of intravenous cefazolin or 2 grams of cefoxitin plus 500 milligrams of metronidazole and repeated 4 hours later during the operation. Intraoperative findings; included resectability, pancreatic tissue structure, pancreatic duct diameter, and length of surgery time.

Definitions of Postoperative Complications

In defining postoperative complications, we used the consensus statements of the International Pancreatic Surgery Working Group on postoperative pancreatic fistula (PPF) and bleeding [16-19]. The threshold required for pancreatic fistula is that the amylase level in the drain fluid accumulated at the head of the pancreas is 3 times the serum amylase level after the 3rd postoperative day. In addition, the definition of PPF should be clinically relevant. Wound

infection was diagnosed according to the guidelines of the US Centers for Disease Control and Prevention [20]. Surgical morbidity severity was classified according to the Clavien-Dindo system and complications of grade 3 and above were accepted as major complications [21,22]. Biliary fistula was defined as any bile leakage from abdominal drains or an intra-abdominal bile collection requiring drainage, and postoperative hemorrhage as more than 200 milliliters of fresh red blood coming from the drain after surgery [23]. Mortality was defined as death during the hospital stay or within 90 days after surgery.

Statistical Analysis

The data obtained in this study were analyzed with the SPSS 21 package program. The Kruskall-wallis H test was used for comparisons with three or more groups. Mann-Whitney U test was used for two-group comparisons. The relationship between categorical variables was analyzed by Chi-Square analysis. 0.05 was used as the significance level. It was stated that there is a significant difference when p <0.05, and no significant difference when p> 0.05.

Results

Of the 122 patients who underwent PD, 76 (62.3%) were male and 46 (37.7%) were female. Of the 122 patients, 47 had NPD, 42 had EBD, and 33 had PBD. There was no significant difference in age between the groups (p> 0.05). The average age was 63 years. Of the 75 patients who underwent BD, 42 (56%) had EBD and 33 (44%) had PBD. The demographic and clinicopathological characteristics of the patients are shown in Table I. There was no significant difference between the groups in terms of gender, comorbidity, and ASA (p>0.05). Intraoperatively; there was also no statistically significant difference in the structure of the pancreatic tissue, pancreatic duct diameter, and operation time (Table I). When the postoperative results were evaluated; a statistically significant difference was observed between the groups in the Clavien-Dindo complication classification (p<0.05). It was detected as grade 3 and above in Group 3 (n = 13, 39.4%), in Group 2 (n = 10, 23.8%) and in Group 1 (n = 3, 6.4%). Grade B and C postoperative pancreatic fistula rate; was statistically significantly higher in Group 2 and Group 3 compared to Group 1 (p<0.05). This rate was higher in Group 3 (n = 13, 39.4%), compared to Group 2 (n = 9, 21.4%) and Group 1 (n = 2, 4.2%). The postoperative bleeding rate was not statistically significantly different between the groups, but it was higher in Group 3 (n = 2, 6.1%). The wound infection rate was not statistically significantly different between the groups, but it was higher in Group 3 (n = 5, 15.2%) and Group 2 (n = 6, 14.3%). There was a statistically significant difference between the groups in terms of postoperative

Table I - *Demographic and clinicopathological characteristics.*

Variables	Grup 1(NBD) (n=47)	Grup 2 (EBD) (n=42)	Grup 3(PBD) (n=33)	P value
Age in years, mean ± SD	61.6 ± 10.9	62.9±12.4	65.2±9.7	0.523
Gender, n (%)				0.404
Male	26 (% 55.3)	27 (% 64.3)	23 (% 69.7)	
Female	21 (% 44.7)	15 (% 35.7)	10 (% 30.3)	
Co-morbidity, n (%)				0.861
None	20 (% 42.6)	14 (% 33.3)	12 (% 36.4)	
1 chronic disease	13 (% 27.7)	12 (% 28.6)	11 (% 33.3)	
2 chronic disease	12 (% 25.5)	15 (% 35.7)	10 (% 30.3)	
≥3 chronic disease	2 (% 4.3)	1 (% 2.4)	0 (% 0)	
ASA, n (%)				0.922
ASA 1	3 (% 6.4)	1 (% 2.4)	1 (% 2.4)	
ASA 2	21 (% 44.6)	20 (% 47.6)	14 (% 42.4)	
ASA 3	23 (% 48.9)	21 (% 50.0)	18 (% 54.5)	
Pathology, n (%)				
Pancreatic cancer	30 (%63.8)	30 (% 71.4)	27 (% 81.8)	
Pancreatic cystic tumor	4 (% 8.5)	3 (% 7.1)	0 (0)	
PNET	3 (% 6.4)	1 (%2.4)	0 (0)	
Ampullary cancer	5 (% 10.6)	0 (0)	1 (%3)	
Duodenal cancer	1 (% 2.1)	1 (% 2.4)	2 (% 6.1)	
Biliary cancer	3 (% 6.4)	5 (% 11.9)	2 (% 6.1)	
Chronic pancreatitis	1 (% 2.1)	2 (% 4.8)	1 (% 3)	
Soft pancreas, n (%)	12 (%25.5)	14 (%33.3)	13 (%39.4)	0.607
MPD, mean ± SD	4.2±2.5	3.7±1.9	4.3±2.4	0.557
Operation time in minute, mean ± SD	371.9±119.1	362.9±142.6	358.8±109.8	0.697

ASA, American Society of Anesthesiologists; PNET, pancreatic neuroendocrine tumor; SD, standard deviation; MPD, main pancreatic duct.

intervention (re-operation + minimally invasive procedure) rate (p<0.05). It was higher in Group 3 (n = 13, 39.4%) compared to Group 2 (n = 10, 23.8%) and Group 1 (n = 3, 6.4%). In addition, the statistically significant re-operation rate (p<0.05) was higher in Group 3 (n = 8, 24.2%) compared to Group 2 (n = 3, 7.1%) and Group 1 (n = 2, 4.3%). There was also a statistically significant difference between the groups in terms of length of hospital stay (p<0.05). The length of hospital stay was shorter in Group 1 than Group 2 and Group 3. In terms of the 90-day mortality rate, there was no significant difference between the groups, but it was higher in Group 3 (n = 3, 9.1%). The results after PD are shown in Table II.

Effectiveness of Timing of The Biliary Drainage

In interval groups; bile drainage was performed in a total of 75 patients, 28 (37.3%) patients in the short group, 27 (36%) in the medium, and 20 (26.6%) in the long group. The postoperative results of these 3 groups are shown in Table III. There was no statistically significant difference in morbidity and mortality between the

Table II - *Postoperative Outcomes*

Variables	Grup 1(NBD) (n=47)	Grup2(EBD) (n=42)	Grup 3 (PBD) (n=33)	P value
Pancreatic fistula				0.007
Biochemical leak	11 (% 23.4)	8 (% 19.0)	5 (% 15.2)	
Grade B	1 (% 2.1)	6 (% 14.3)	5 (% 15.2)	
Grade C	1 (% 2.1)	3 (% 7.1)	8 (% 24.2)	
PPH				1
Wound infection	2 (% 4.3)	2 (% 4.8)	2 (% 6.1)	0.422
	3 (% 6.4)	6 (% 14.3)	5 (% 15.2)	
Clavien-Dindo classification				0.0001
Grade 1	25 (% 53.2)	9 (% 21.4)	12 (% 36.4)	
Grade 2	19 (% 40.4)	23 (% 54.8)	8 (% 24.2)	
Grade 3 ≥	3 (% 6.4)	10 (% 23.8)	13 (% 39.4)	
Postoperative intervention				0.003
MIP	1 (% 2.1)	7 (% 16.7)	5 (% 15.2)	
Reoperation	2 (% 4.3)	3 (% 7.1)	8 (% 24.2)	
Hospital stay, mean ± SD	15.9±9.9	19.9±9.1	23.3±12.2	0.003
90-day mortality	1 (% 2.1)	2 (% 4.8)	3 (% 9.1)	0.442

PPH, postpancreatectomy hemorrhage; MIP, minimally invasive procedure; SD, standard deviation.

Table III - *Postoperative results of interval time groups*

Variables	Short (n = 28)	Intermediate (n = 27)	Long (n = 20)	P value
Clavien-Dindo classification				0.295
Grade 1	10 (% 35.7)	7 (% 25.9)	4 (% 20.0)	
Grade 2	8 (% 28.6)	11 (% 40.7)	12 (% 60.0)	
Grade 3 ≥	10 (% 35.7)	9 (% 33.3)	4 (% 20.0)	
Pancreatic fistula				0.842
Biochemical leak	5 (% 17.9)	5 (% 18.5)	3 (% 15.0)	
Grade B	4 (% 14.3)	5 (% 18.5)	2 (% 10.0)	
Grade C	6 (% 21.4)	3 (% 11.1)	2 (% 10.0)	
PPH	2 (% 7.1)	1 (% 3.7)	1 (% 5.0)	1
Wound infection	3 (% 10.7)	6 (% 22.2)	2 (% 10.0)	0.452
Postoperative intervention				0.584
MIP	4 (% 14.3)	6 (% 22.2)	2 (% 10.0)	
Reoperation	6 (% 21.4)	3 (% 11.1)	2 (% 10.0)	
Hospital stay, mean ± SD	21± 12.5	21± 9.6	22.4± 9.7	0.507
90-day mortality	2 (% 7.1)	2 (% 7.4)	1 (% 5.0)	1

PPH, postpancreatectomy hemorrhage; MIP, minimally invasive procedure; SD, standard deviation.

groups. However, in the Clavien-Dindo complication classification, there were 10 (35.7%) grade 3 and above complications in the short group, 9 (33.3%) in the medium group, and 4 (20.0%), the lowest, in the long group. Grade B and C postoperative pancreatic fistula rates; were found to be less in the long group 4 (20%) (in the short and medium groups; 10 (35.9%) and 8 (29.6%), respectively). The postoperative bleeding rate; was higher in the short group with 2 (7.1%), while it was 1 (3.7%) and 1 (5%) in the medium and long groups, respectively. The wound infection rate was less in the long group with 2 (10%), while it was 3 (10.7%) in the short group and 6 (22.2%) in the middle group. Postoperative intervention (re-operation + minimally invasive procedure) rate; was the highest in the short group with 10 (35.9%), while it was 9 (33.3%) and 4 (20%) in the medium and long group, respectively. There was no statistically significant difference between the groups in terms of length of hospital stay and 90-day mortality.

Discussion

Despite the increasing diagnosis and treatment methods in periampullary region tumors, clinical characteristics of the patient at the time of admission may affect perioperative complications. The level of jaundice at the time of admission, liver function tests, and especially the presence of cholangitis can complicate pancreaticoduodenectomy, which has a high risk of complications and can significantly increase postoperative morbidity [24,25].

The management of BD in patients with a diagnosis of resectable periampullary tumor scheduled for PD is still controversial. Old studies argued that BD can reduce the risk of infection by enhancing the immune system and can improve postoperative outcomes [26,27].

In the study conducted by Van der Gaag et al, it was emphasized that early surgery without BD does not increase the risk of complications [3]. Nevertheless, Feng Yang et al. reported that BD did not increase surgical morbidity after PD [28]. In our study; it was determined that BD increased surgical morbidity after PD, but did not cause a significant difference in mortality.

Conflicting results published in the literature; may be due to differences such as the number of patients, demographic and clinicopathological characteristics, BD type, and duration. Current recommendations for BD; include patients who will receive neoadjuvant therapy, acute cholangitis, delayed surgery for technical reasons, severe hyperbilirubinemia, and alleviation of cholestasis [29].

The choice of the most appropriate method (endoscopic or percutaneous) for biliary drainage is a matter of debate. Generally, the patient is referred to surgery after the drainage procedure is performed in gastroenterology or other internal departments, without leaving the choice to the surgical team. We usually plan direct surgery if the bilirubin level is below 10mg/dl and there is no obstacle to surgery. Both technical methods have advantages and disadvantages. The choice of technique may vary according to the surgeon's preference and the experience of the center. In fact, both methods are techniques that complement each other. Both technical methods can be applied skillfully in our hospital. In PBD, besides a high success rate in palliative relief of cholestasis and a lower risk of cholangitis; bleeding, portal vein thrombosis, catheter tract implantation metastasis, and poor patient comfort have been reported as well [30,31]. In our clinic, surgery could not be performed due to the detection of liver metastases in 2 patients after PBD. Nonetheless, detection of less inflammation and edema in the operation field provides convenience to the surgeon. EBD is considered a less invasive technique. However, the risk of procedural complications such as bacterial contamination from the intestine, duodenal perforation, stent obstruction, pancreatitis, and increased inflammation and edema at the surgical site increases [30]. On the other hand, although naso-biliary drainage is a good alternative for stent obstruction in patients who will be scheduled for surgery in the short term, patient comfort decreases in the meanwhile.

There are not enough randomized controlled studies to compare bile drainage methods, and the results are also inconsistent. Speer et al. argued that endoscopic drainage is superior to percutaneous drainage in patients with unresectable, especially distal bile duct obstruction [4]. Ho, et al. reported in their study that metallic stents placed percutaneously lead to better results than plastic stents placed endoscopically [32]. In a different meta-analysis; the overall complication rate, pancreatitis rate, and 30-day mortality of the two procedures have been shown to be similar [33]. In our study; grade 3 and above complications in the Clavien-Dindo complication classification were determined to be higher in the PBD group than EBD (39.4% vs 23.8%). Similarly, the re-operation rate was determined to be higher in the PBD group compared to EBD (24.2% vs 7.1%). However, there was no significant difference regarding the 90-day mortality.

Although BD is widely applied in many centers, the optimal duration of BD is unclear and there are very few clinical studies on this subject. Animal studies and experimental data have recommended BD for at least 4-6 weeks for recovery of hepatic function [34]. In short-term drainage, sufficient time may not be provided for liver functions to return to normal. However, long-term drainage; can cause stent occlusion, migration, infection, and tumor progression. Son et al. evaluated 120 patients with a diagnosis of periampullary tumor, and 66 of these patients received short-term (< 2 weeks) and 54 of the patients long-term (> 2 weeks) BD [35]. While morbidity and mortality did not differ between the 2 groups, it was reported that BD-related complications were significantly less in patients in the short-term group (< 2 weeks). Sandini et al. reported that the short-term

of BD (< 4 weeks) was associated with increased major morbidity, biliary fistula rate, and infectious complications [36]. There are also studies showing that some physiological functions may not return to normal even after 6 weeks of drainage [15,37]. In our study, when the interval groups were evaluated, it was determined that there was no statistically significant difference between the groups in terms of morbidity and mortality. However, in the long interval group, we found that the rate of grade B and C fistula was lower, along with a grade 3 and higher complication rate in the postoperative Clavien-Dindo classification.

Conclusion

In our study, we determined that the postoperative morbidity rate was higher in patients who underwent preoperative biliary drainage compared to patients without drainage. Postoperative grade B and C fistula complications increase, especially in patients with biliary drainage, and therefore the management of patients becomes difficult. On the other hand, in patients who were operated in the long interval after biliary drainage, Grade 3 and higher complications and Grade B and C fistula complications were less common in the Clavien-Dindo classification after PD. Therefore, we think that EBD should be preferred when preoperative biliary drainage is required and it is appropriate to plan the surgery at least six weeks after drainage.

Riassunto

Obiettivo dello Studio: Confrontare i risultati di morbilità e mortalità postoperatoria in pazienti con e senza drenaggio biliare transepatico endoscopico e percutaneo per ittero ostruttivo da tumore periampollare ed esaminare l'effetto degli intervalli fino all'intervento chirurgico sulla morbilità e mortalità postoperatoria in pazienti sottoposti a drenaggio biliare preoperatorio (BD).
Metodi: I pazienti sono stati divisi in 3 gruppi in base al loro stato di BD. Gruppo1, senza drenaggio biliare (NBD), Gruppo2, Drenaggio biliare endoscopico (EBD), Gruppo3, Drenaggio biliare transepatico percutaneo (PBD). I pazienti sottoposti a drenaggio biliare prima della pancreaticoduodenectomia (PD) sono stati suddivisi in 3 intervalli in base all'intervallo di tempo tra il drenaggio e l'intervento chirurgico: breve intervallo; pazienti sottoposti a intervento chirurgico in 21 giorni e <, Intervallo medio; tra 22-42 giorni, intervallo lungo; 43 giorni e >. Gruppi e intervalli sono stati confrontati in termini di morbilità e mortalità postoperatoria.
Risultati: Dei 122 pazienti sottoposti a PD, 76 (62,3%) erano maschi e 46 (37,7%) erano femmine. All'interno di questi pazienti, 47 (38,52%) avevano NPD, 42 (34,42%) avevano EBD e 33 (27.,05%) avevano PBD. Il tasso di fistole postoperatorie di grado B e C era più alto nei gruppi sottoposti a drenaggio preoperatorio rispetto al gruppo senza drenaggio preoperatorio (p = 0,007).
Conclusione: Si è riscontrato che il tasso di complicanze postoperatorie era inferiore nei pazienti non sottoposti a BD rispetto ai pazienti sottoposti a drenaggio biliare. Inoltre, è stato osservato che il metodo di drenaggio endoscopico è associato a meno complicazioni rispetto al metodo di drenaggio percutaneo transepatico.

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