Impact of Preoperative Endoscopic Biliary Drainage on Postoperative Outcome after Pancreaticoduodenectomy

Hazem M Zakaria¹, Nahla K Gaballa², Mohammed Abbas³, Osama Elbahr⁴, Talaat Zakareya⁴

Corresponding author:

Hazem Mohamed Zakaria, MD
Department of Hepatopancreatobiliary
& liver transplantation surgery
National Liver Institute
Menoufia University
32511 Shebin El-koom, Menoufia, Egypt
E-mail: hazemlasheenn@yahoo.com
Tel: +2 01097071055
Fax: +20482234586
Tel.: +20482222740

¹Department of Hepatopancreatobiliary and Liver Transplant Surgery, National Liver Institute, Menoufia University, Menoufia, Egypt

²Department of Anesthesia and Intensive Care, National Liver Institute, Menoufia University, Menoufia, Egypt

³Department of Diagnostic and intervention radiology, National Liver Institute, Menoufia, Egypt

⁴Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Menoufia, Egypt

ABSTRACT

Background: The value of preoperative biliary drainage (PBD) on the surgical outcome after pancreaticoduodenectomy (PD) is still a point of controversy. The aim of this study was to identify the impact of biliary drainage (BD) prior to PD on the postoperative outcome.

Methods: The data of patients, who underwent PD from February 2009 to February 2017, were retrospectively studied. A comparison was performed between 2 groups of patients; group A (with PBD) and group B (without PBD), according to preoperative, operative and post-operative data.

Results: PD was performed in 158 patients with periampullary lesions. Group A, included 76 patients (48.1%) while 82 patients were included in group B (51.9%). The incidence of major postoperative complications was significantly higher in group A ($P=0.04$). The infectious complications were higher in group like; positive intraoperative bile culture ($P=0.06$), intra-abdominal abscess ($P=0.07$) and wound infection ($P=0.04$). Also, hospital stay and mortality were higher in group A ($P=0.05$ and 0.08 , respectively). High preoperative bilirubin level was not a risk factor for major postoperative complications ($P=0.12$).

Conclusion: Patients with PBD had a significantly higher incidence of major postoperative complications mainly of infectious ones, thus PBD should be performed only in selected patients, not as a routine prior PD.

Key words: biliary drainage, pancreaticoduodenectomy, postoperative complications, wound infection

INTRODUCTION

Periampullary lesions can be the cause of obstructive jaundice (OJ), pancreaticoduodenectomy (PD) being usually the curative choice, especially for malignant obstruction. OJ with high serum bilirubin level is a risk factor for cholangitis, cardiac or liver dysfunction, and coagulation profile affection. Theoretically, biliary drainage (PD) with reduced bilirubin level can improve liver

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function and the outcome after surgery. However, there is still controversy over the use of preoperative biliary drainage (PBD) before PD (1,2).

Some literature showed the improved results of surgery with PBD. Others reported no effect or there was an increase in postoperative complications (infectious complications, delayed gastric emptying, biliary or pancreatic fistula), hospital stay and mortality, with an end result of increasing the cost of surgery. Thus some centres do not recommend PBD to be a routine before resectable tumour and reserve it for severe hyperbilirubinemia or cholangitis (3-5).

Biliary drainage can be done either by endoscopic retrograde cholangiopancreatography (ERCP), endoscopic nasobiliary drainage (ENBD), or percutaneous transhepatic drainage (PTD), with reported different surgical outcomes with the use of each technique (6-8). The aim of this study was to show the effect of preoperative endoscopic biliary drainage (EBD) on postoperative morbidity and mortality after PD surgery.

PATIENTS AND METHODS

Patients

A retrospective study was conducted for patients who underwent PD between February 2009 and February 2017 at the National Liver Institute, Menoufia University, Egypt. The data were collected after institutional review board approval.

ERCP was the method of BD in this study. Our patients were divided into 2 groups; group A (with PBD) and group B (without PBD). Patient demographics, preoperative, operative and postoperative clinico-pathological data were collected, analyzed and compared between the 2 groups.

Operative Details

PD was performed for periampullary lesions (either benign or malignant). Classic PD or pylorus-preserving PD (PPPD) were included in the study. Pancreatic anastomosis was performed by pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) (either duct to mucosa or jejunal loop invagination). The pancreatic texture was assessed by surgeon experience and pancreatic duct diameter was calculated.

Postoperative follow up

The early postoperative complications were assessed by the Clavien-Dindo classification of surgical complica-

tions (9) from I to V, depending on the main complications of each patient. Complications $\geq$ grade IIIa were considered as major complications. Postoperative complications like biliary leakage, postoperative pancreatic fistula (PPF), post pancreatotomy haemorrhage (PPH), and delayed gastric emptying and their grades were defined and classified according to the International Study Group of Pancreatic Surgery (ISGPS) definitions and grading (10-12). The postoperative follow up of the patients was from the day of surgery to February 2018 with a mean follow up period of 43 months.

Statistical Analysis

The analysis of the data was performed using SPSS version 21.0 (Chicago, IL, USA). The comparison between categorical variables was performed by Fisher's exact test or χ^2 -test. In continuous variables, the differences between the means were compared by independent-sample T-test or Mann-Whitney U test. Independent risk factors for major postoperative complications were assessed in multivariate analysis using linear regression model. Significant P value was considered when <0.05 .

RESULTS

Pancreaticoduodenectomy was performed in 158 patients with periampullary lesions (malignant and benign). Group A, included 76 patients (48.1%) while 82 patients (51.9%) were included in group B. In group A, 48 patients (63.2%), underwent biliary drainage before the surgical consultation, mainly the early cases. The indications of ERCP in other patients were a very high bilirubin level affecting liver function, cholangitis, and/or delay in the elective surgery.

The complications after ERCP were: stent dysfunction and pancreatitis in 20 patients (26.3%), bleeding in 5 patients (6.6%) and duodenal perforation in 2 patients (2.6%); most of these complications delayed the PD operation. The mean duration between PD and the surgery was 5.5 weeks (range, 2-34 weeks).

The two groups were compared regarding the patient demographics, preoperative and operative data (*table 1*). Univariate analysis presented a significant difference between both groups regarding gender ($P=0.01$), preoperative total bilirubin level ($P=0.04$) and operative blood loss ($P=0.03$). Serum level of carbohydrate antigen (CA) 19.9, and positive lymph nodes (LNs), were higher in group A, but without a statistically significant difference ($P=0.07$).

The overall incidence of postoperative complica-

Table 1 - Patients characteristics, preoperative, operative and pathological data

	PBD (n=76)	No-PBD (n=82)	P-value
Age (y)			0.36
mean±SD	55.6±12	57.1±13.6	
(range)	(35-74)	(20-75)	
age >60	33(43.4%)	39(47.6%)	0.63
Male Gender	49(64.5%)	33(40.2%)	0.01
Body mass index (kg/m²)			0.87
≤25	36(47.4%)	38(46.3%)	
>25	40(52.6%)	44(53.7%)	
Co-morbidities (yes)	48(63.2%)	47(57.3%)	0.12
DM	39(51.3%)	40(48.8%)	0.52
HTN	29(38.2%)	32(39%)	0.83
Cardiovascular disease	13(17.1%)	17(20.7%)	0.33
Main symptoms			
Jaundice	58(76.3%)	36(43.9%)	0.01
Abdominal pain	31(40.8%)	44(53.7%)	0.11
Nausea/vomiting	24(31.6%)	26(31.7%)	1.0
Loss of weight	40(52.6%)	39(47.6%)	0.35
Prestenting total bilirubin (mg/dl)			0.01
mean±SD	12.3±6.2	4.8±7.1	
(range)	(5.4-38)	(0.6-16)	
Preoperative total bilirubin (mg/dl)			0.04
mean±SD	3.3±4.3	4.8±7.1	
(range)	(0.5-13.6)	(0.6-16)	
ALT (U/L)			0.12
mean±SD	47±27	58±29	
(range)	(24-153)	(28-165)	
Albumin (g/dl)			0.38
mean±SD	3.5±0.5	3.6±0.5	
(range)	(2.9-4.4)	(3-4.8)	
White blood cells (×10⁹/L)			0.17
mean±SD	7.8±2.2	6.5±2.7	
(range)	(4-12.6)	(5-13)	
CA 19-9 (U/mL)			0.09
mean±SD	1568±6373	177±312	
(range)	(13-37530)	(8-2000)	
normal	34(44.7%)	40(48.8%)	
high	42(55.3%)	42(51.2%)	
Pancreatic texture			0.18
Firm	39(51.3%)	38(46.3%)	
soft	37(48.7%)	44(53.7%)	
Type of pancreatic reconstruction			0.15
Pancreaticogastrostomy	15(19.7%)	8(9.8%)	
Pancreaticojejunostomy	61(80.3%)	74(90.2%)	
-invagination	28(45.9%)	39(52.7%)	
-duct to mucosa	33(54.1%)	35(47.3%)	
Vascular reconstruction			1.0
yes	9(11.8%)	10(12.2%)	
Operative time (min)			0.16
mean±SD	410±110	365±125	
(range)	(250-670)	(240-550)	
Operative blood loss			0.03
mean±SD	900±550	600±500	
(range)	(250-2500)	(200-2000)	
Blood transfusion (unit)			0.46
mean±SD	1±2	1±1	
(range)	(0-8)	(0-6)	
Pathological diagnosis			0.46
Malignant	59(77.6%)	59(72%)	
Benign	17(22.4%)	23(28%)	
Pathological site			0.09
Pancreas	49(64.5%)	57(69.5%)	
Ampullary	16(21.1%)	18(22%)	
Duodenum	2(2.6%)	5(6.1%)	
CBD	9(11.8%)	2(2.4%)	

Pathological tumour type			0.13
PDAC	33(43.4%)	30(36.6%)	
Ampullary adenocarcinoma	16(21.1%)	18(22%)	
Cholangiocarcinoma	8(10.5%)	2(2.4%)	
NET	3(3.9%)	5(6.1%)	
IPMN	3(3.9%)	5(6.1%)	
Cystic tumour	3(3.9%)	7(8.5%)	
Other types	10(13.3%)	15(18.3%)	
Tumour differentiation in malignant cases (n=59 for each group)			0.25
Well	14(23.7%)	10(17%)	
Moderate	31(52.6%)	32(54.2%)	
Poor	14(23.7%)	17(28.8)	
Maximum tumour diameter			0.34
Mean±SD	3.3±2.2	3.1±2.6	
(Range)	(1.3-9)	(1.5-8)	
Positive LNs			0.07
Mean±SD	2±1	1±2	
(Range)	(0-8)	(0-4)	
yes	32/59(45.2%)	22/59(37.3%)	

DM (diabetes mellitus), HTN (hypertension), SD (standard deviation), ALT (alanine aminotransferase), CA (Carbohydrate antigen), LNs (lymph nodes), PDAC (pancreatic duct adenocarcinoma), NET (neuroendocrine tumours), IPMN (intraductal papillary mucinous neoplasm)

tions was higher in group A (table 2), with a significant statistical difference in major postoperative complications ($P=0.04$). The infectious postoperative complications were higher in group A including: positive intra-operative bile culture [mainly for *Escherichia coli* (*E-coli*)

and *Klebsiellapneumoniae*], intra-abdominal abscess (IAA) formation ($P=0.07$), however without a statistical significant difference, and wound infection (WI) ($P=0.04$). Delayed gastric emptying was significantly different between both groups ($P=0.03$). In group A, hospital stay

Table 2 - postoperative data and complications

Variables	PBD (n=76)	No-PBD (n=82)	P-value
Clavien-Dindo classification of surgical complications			0.29
0	16(21.1%)	21(25.6%)	
I	16(21.1%)	18(22%)	
II	20(26.3%)	28(34.1%)	
IIIa	9(11.8%)	7(8.5%)	
IIIb	4(5.3%)	3(3.7%)	
IVa	0	1(1.2%)	
IVb	2(2.6%)	2(2.4%)	
V	9(11.8%)	2(2.4%)	
Post operative major complications (≥IIIa)	24(31.6%)	15(18.3%)	0.04
Post operative main complications			
- intra-abdominal abscess	11(14.5%)	3(3.7%)	0.07
- pancreatic fistula	13(17.1%)	11(13.4%)	0.25
A	8	5	
B	3	4	
C	2	2	
- delayed gastric emptying	8(10.5%)	18(22%)	0.03
A	4	10	
B	2	5	
C	2	3	
- postpancreatectomy haemorrhage	4(5.3%)	6(7.3%)	0.77
A	0	1	
B	2	3	
C	2	2	

- wound infection	21(27.6%)	13(15.9%)	0.04
- biliary fistula5(6.6%)	3(3.7%)	0.18	
- gastric fistula	3(3.9%)	1(1.2%)	0.48
- Positive bile culture	11/43 (25.6%)	3/22(13.6%)	0.06
- medical complications (pulmonary, cardiac, renal,...)	15 (19.7%)	9(11%)	0.15
Reoperation	8(10.5%)	5(6.1%)	0.14
ICU stay (days)			0.25
mean±SD	5±5	3±6	
(range)	(0-18)	(0-11)	
Hospital stay (days)			0.05
mean±SD	14±11	10±7	
(range)	(8-58)	(6-43)	
Rehospitalization in first 3 ms	4(5.3%)	2(2.4%)	0.25
Hospital mortality	9(11.8%)	2(2.4%)	0.08
Recurrence of tumour	15/59(25.4%)	19/59(32.2%)	0.29

ICU (intensive care unit), SD (standard deviation)

was significantly higher ($P=0.05$), and also hospital mortality, but without a statistical significant difference ($P=0.08$).

The risk factors for postoperative major complications (table 3) were: PBD ($P=0.03$), the high serum level of CA19.9 ($P=0.03$), soft pancreatic texture ($P=0.02$), operative blood loss ($P=0.01$), perioperative blood transfusion ($P=0.03$), positive LNs in histopathology ($P=0.04$). In multivariate analysis the independent risk factors for major postoperative complications were high CA19.9 ($P=0.034$) (HR=1.2; 95% CI: 0.82-1.7), and operative blood loss ($P=0.042$) (HR=1.0; 95% CI: 0.92-1.1). High preoperative bilirubin level (>15 mg/dl) was not a risk factor for major postoperative complications ($P=0.12$).

The hospital mortality rate was as follows: in patients with PBD 11.8%, and in patients without PBD 2.4% ($P=0.08$).

DISCUSSION

Patients with OJ have a high risk of bacterial translocation with endotoxemia and inflammatory cascades which can alter the cardiac, hepatic or renal function (1,13).

Whether to perform or not PBD for patients with OJ is still a debatable point. Many retrospective and prospective literature studies discussed this issue with different conclusions (13-15). Experimental studies had shown that reduction of serum bilirubin level can improve the liver and immune system function with correction of the coagulation profiles (15,16). Liu et al, showed that serum bilirubin did not significantly affect postoperative complications after PD (17) as reported in our study. In contrast, Smith et al reported that the high preoperative bilirubin level had negative feedback

on early postsurgical outcome (18). The threshold level of bilirubin which may need PBD for better prognosis after surgery is still in need of further large volume studies. In this study bilirubin level >15 mg/dl has no negative impact on postoperative complications.

Several early retrospective and meta-analysis studies comparing preoperative biliary stenting or the lack of it showed that there was no difference in postoperative outcome regarding different complications or hospital mortality (19,20). But later meta-analyses showed the increased incidence of infectious complications (6, 14) as shown in our study. Some studies noticed that nearly 42-79% of patients with PBD underwent the drainage procedure by the gastroenterologist before evaluation or consultation of the surgeon (13,21), as seen in our early cases, but in last 3 years of this study there was established OJ meeting and board for discussion of these patients with OJ and selection of the proper management plan for each case.

Singhirunnusorn et al, proved a no significant difference in mild and major complications of patients with PBD (42% and 37%, respectively) in comparison to (35% and 32.8% respectively) in patients without PBD. They also reported no significant difference in hospital mortality, and each complication alone like biliary fistula, pancreatic fistula, WI, and reoperation (22,23). In contrast to our study with a significant difference in major complications, but maybe the definition of major complications that made these changes of results between the different studies. Liu et al, also reported no significant difference in any of the complications between both groups of patients with PBD and without PBD with moderate increase of; positive bile culture (12.8% vs 5.9%, respectively), IAA (17% vs 11.8%) and

Table 3 - Potential risk factors for major postoperative complications

	Major complications (n=39)	No and minor complications (n=119)	P-value
age >60	22(56.4%)	50(42%)	0.12
Male Gender	16(41%)	66 (55.5%)	0.08
Body mass index (kg/m ²) >25	24(61.5%)	60(50.4%)	0.27
Co-morbidities (yes)	25(66.7%)	70(58.8%)	0.7
Preoperative total bilirubin (mg/dl). mean±SD	1.8±1.9	3.8±4.6	0.07
Total bilirubin > 15 mg/dl	3(7.7%)	21(17.6%)	0.12
Preoperative biliary drainage	25(64.1%)	51(42.9%)	0.03
ALT (U/L) mean±SD	52±29	49±36	0.31
Albumin (g/dl) mean±SD	3.5±0.6	3.7±0.5	0.42
White blood cells (×10 ⁹ /L)	8.2±2.6	7.5±1.8	0.23
CA 19-9 (U/mL) mean±SD	2109±8468	427±1390	0.03
Pancreatic texture soft	27(69.2%)	54(45.4%)	0.02
Pancreatic duct diameter < 3 mm	9 (23%)	22(18.5%)	0.18
Type of pancreatic reconstruction			0.60
Pancreaticogastrostomy	7(17.9%)	16(13.4%)	
Pancreaticojejunostomy	32(82.1%)	103(86.6%)	
Vascular reconstruction yes	8(20.5%)	11(9.2%)	0.08
Operative time (min)	415±125	380±110	0.12
Operative blood loss mean±SD	1100±650	800±500	0.01
Blood transfusion yes	29(74.4%)	65(54.6%)	0.03
Pathological diagnosis			0.19
Malignant	26(66.7%)	92(77.3%)	
Benign	13(33.3%)	27(22.7%)	
Tumour differentiation in malignant cases			0.36
Well	7(26.9%)	17(18.5%)	
Moderate	13(50%)	50(54.3%)	
Poor	6(23.1%)	25(27.2%)	
Maximum tumour diameter Mean±SD	2.9±2.4	3.1±2.5	0.28
Positive LNs yes	15/26(57.7%)	39/92(42.4%)	0.04

SD (standard deviation), ALT (alanine aminotransferase), CA (Carbohydrate antigen), LNs (lymph nodes).

WI (14.9% vs 8.7%, respectively) (17). The average incidence of WI in some literature studies was 5.5% - 21.5% (22,24).

In contrast to previous studies, Van der Gaag et al, reported in their randomized controlled trial that the incidence of severe complications was 74% in patients with endostenting versus 39% in patients with early surgery without PBD, but most of these complications were due to the procedure of ERCP, not to postsurgical complications (3). Also, Ng et al, reported a high incidence of overall infectious complications in the

group of PBD than the other group without drainage (77% versus 67%, respectively). Wound infection was the highest complication (41%) of the infectious ones, followed by IAA (29%) (16), as observed in our study. But we had a lower incidence of infectious complications than the former study.

The optimal duration of BD before PD is still unclear. In one of the animal studies, the optimal time for restoration of most of the hepatic functions, biliary epithelium and immune system functions was 4-6 weeks, even if bilirubin has decreased to its normal

levels before this duration. So the short period of PBD may be the cause of failure of biliary stenting to improve the outcome after the operation. Also, the long duration of biliary stenting has its drawbacks of increased liability of repeated attacks of cholangitis, bacterial colonization, inflammation and fibrosis in the wall of the bile duct with a subsequent more difficult operation and a higher incidence of biliary leakage (15,25). Many studies observed polymicrobial organisms in bile cultures withdrawn during the surgery in patients with biliary stenting. *E-coli* and *Klebsiellapneumoniae* were the most common bacterial infection (16,26) as reported in our study. Other large volume studies are needed for the justification of the optimal time of PD needed before surgery to have a better outcome.

Another debatable issue is the best method of BD: whether internal by endoscopy or external by PTD. Kitahata et al, reported that PTD has the least post-operative complications than ENBD and ERCP. But PTD has its disadvantages of stent displacement or external tube traction by the patient, and a relative risk of increased tumour seedling (27). One of meta-analysis discussed the complication of ERCP that was used for PBD and demonstrated that 27.4% of the patients had complications related to the procedure and may be the cause of the surgical delay, and 33.8% had stent dysfunction prior to PD and most of them needed stent replacement (13,14). We had nearly percentages of ERCP complications as seen in the previous study. Also, the type of the stent either plastic or covered metallic stent may affect the outcome, with better results for the metallic stent for long waiting before PD as in patients with neoadjuvant chemotherapy (28,29).

CONCLUSION

In conclusion, patients with PBD still have the risk of ERCP complications that may delay the time of elective surgery. PBD had significantly higher incidence of major postoperative morbidity mainly of infectious complications and higher hospital mortality. PBD should be performed only in selected patients as in cases with cholangitis or severe hyperbilirubinemia not as a routine before PD. Preoperative high bilirubin level is not a risk factor for postoperative complications and should not be a contraindication for surgery.

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